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Some Clinical Features of Complete Heart Block

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A review was made of 251 cases of complete heart block. They were divided into the following groups: coronary artery disease (nonacute), 58 cases; myocardial infarction (acute), 49 cases; hypertensive heart disease, 62 cases; rheumatic heart disease, 21 cases; miscellaneous, 16 cases; "etiology undetermined," 18 cases; and digitalis intoxication, 27 cases. Among the various clinical features analyzed were the sex and age factors, the occurrence of syncope, palpitation, congestive failure, anginal pain, and the duration of life after the onset of major symptoms. Methods of treatment are discussed.

THE clinical course of patients with complete heart block, with or without attacks of Adams-Stokes syncope, is very variable. Events are often unpredictable. Some live a short time, others may carry on for a great many years. The causes of the underlying defect are numerous and the circumstances under which the major symptoms arise vary greatly. Even the nomenclature is somewhat confusing. A sudden total arrest of the heart when there is no evidence of conduction de[f] may be called an episode of Adams-Stokes s[y]cope by one observer and not by another. The very mechanism of fainting is also different in different individuals. Although much has been written about this subject, it seemed worth while to analyze in greater detail some of the specific features of complete heart block. An attempt was made particularly to see if there were distinct differences in the course of events and in the findings when heart block developed under one set of circumstances, such as coronary artery disease in contrast to valvular disease, or when no definite etiology could be determined.

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In reviewing the very extensive literature on complete heart block comprising over 200 publications, only a few seem to be pertinent for the purposes of this study. One of the first to divide the attacks of syncope into two types was Schwartz.[1, 2] This was more clearly discussed and differentiated by Parkinson, Papp, and Evans.[3] Somewhat later a review was made by White and his associates.[4, 5]

Scope and Materials

Patients who manifested only first or second degree atrioventricular block with or without syncope were not included. Similarly, cases of atrioventricular dissociation typified by "interference dissociation or ventricular capture phenomenon" were excluded. These were all cases in which the ventricular rates were more rapid than the atrial rates. Furthermore, syncopal attacks associated with standstill of the sinus node or atrial mechanism were also excluded if no evidence of atrioventricular block was present. The only cases forming the basis for this study were those which at one time or another had third degree atrioventricular block in which the ventricular rate was slower than the atrial rate. In most instances, the atria were contracting independently of the ventricles, though atrial fibrillation was present in 43 cases, excluding the digitalis intoxication group. In many, first degree or second degree heart block had occurred at one time or another. In 92 per cent of the cases the diagnosis of complete heart block was verified by electrocardiograms. In the other 8 per cent the diagnosis on clinical grounds seemed quite certain. With these

restrictions, there were 251 cases available for investigation. One hundred fifty-three were obtained from the records of the Peter Bent Brigham Hospital during the years 1913 to 1955, and 98 cases were from the consultation practice of one of us.

Clinical Picture

Complete heart block is generally associated with a slow ventricular rate, i.e., 30 or 40 beats per minute. Occasionally, the heart rate may be 50 or 60 beats per minute or a little greater. The bradycardia may be initiated suddenly by an attack of syncope. In others, a slow heart rate is suddenly observed without any significant change in the symptomatology or awareness of the change in rhythm. There are numerous instances in which syncopal attacks occur and with recovery the heart returns rather promptly to a normal sinus rhythm. In such cases, an asystole has taken place, accounting for the spell of unconsciousness, and is followed for only a short time by varying degrees of atrio-ventricular heart block.[6] In a few minutes a normal sinus rhythm is established without evidence of conduction defect. These cases generally display more permanent complete heart block some months later. Before this is apparent, they present puzzling problems and may be misinterpreted as instances of hysteria, benign syncope, or epilepsy. In some of these cases minor clues may be found that direct the observer's attention to the true nature of the condition; these include complete or incomplete bundle branch block or a full P-R interval of 0.20 to 0.22 second. In these puzzling cases, the physician would do well to make every effort to observe the actual episode; for during those brief moments, the diagnosis may be quite obvious. Another clue in this regard is obtained by carotid sinus stimulation. If as a result of this test the heart slows and a temporary transient complete atrioventricular dissociation results, it is very likely that permanent complete heart block may develop at some later date. The inference from the above is that for some period of time, patients may have a normal sinus rhythm after a syncopal attack and yet be suffering from Adams-Stokes episodes, and only later manifest permanent complete heart block.

The symptoms due to complete block itself are very few. The slow ventricular rate of 30 does not necessarily produce pain, dyspnea, or significant prolonged weakness. The patient may suddenly become aware that the heart is beating slowly, and this may be his first complaint to the physician. In a fair number, palpitation may be a primary symptom. More often momentary weakness, dizziness, or actual spells of unconsciousness are the major difficulties. In some, profound weakness, prostration, and even a prolonged state of semiconsciousness may result when the heart continues to beat regularly, but extremely slowly, i.e., 15 to 20 times per minute. The duration of actual syncope will depend upon the length of ventricular asystole. If this lasts two to three seconds the patient may have a feeling of a wave passing over him, with a momentary sense of uncertainty or blankness, just like a petit mal. If it lasts several seconds and the patient is standing or walking, he will drop to the ground, regaining consciousness immediately, having no idea of what has happened. If the asystole continues longer, convulsive movements appear with stertorous breathing. After half a minute or more, if the heart does not resume its beats, the patient may appear to be dead, without either cardiac or respiratory function. Occasionally during such long intervals, the continuing contractions of the atria may still be visibly displayed in faint pulsations of the jugular vein. Finally, if the heart does not resume its beat in several minutes, death occurs. On the other hand, it is amazing how instantaneously consciousness is restored if the heart does start contracting; in fact, after one or two beats the patient may resume the previously interrupted conversation.

The diagnosis of complete heart block is generally a simple matter. Apart from the history of the symptoms mentioned above, physical examination in the great majority of cases reveals distinctive objective findings. On auscultation of the heart the rate is generally slow and regular, 30 to 40 beats per minute. Not infrequently, this regular rhythm may be interrupted by premature beats. The single most valuable and almost pathognomonic sign is the changing intensity of the first heart sound heard best at the apex with a regular slow beat.

In some instances it will be necessary to listen as long as one-half to a whole minute before the loud first sound appears (bruit de canon). With other cycles the first sound may be muffled, faint, or of average intensity. This pathognomonic sign will be absent in cases of complete heart block with atrial fibrillation, as the first sound will then be constant in its intensity. A second sign is the detection of faint atrial sounds during the long diastolic intervals. These are more audible in the early than in the late portion of diastole and are heard best between the apex and lower sternum. Occasionally these atrial contractions will produce visible, faint pulsations in the jugular pulse. A more distinctive phenomenon to be observed in the neck is the detection of occasional, sudden, large pulsations in the jugular vein, produced by the simultaneous contraction of the atria and ventricles. Finally, it will be difficult in most cases to alter the ventricular rate by carotid sinus stimulation.

Classification of Cases

Among the 251 cases in this study, there were 58 (23 per cent) with coronary artery disease (nonacute), 49 (19 per cent) of acute myocardial infarction, 62 (24 per cent) with hypertensive heart disease, 21 (10 per cent) with rheumatic heart disease, 16 (6 per cent) with rare forms of heart disease (miscellaneous), 18 (7 per cent) in which the etiology was not known, and 27 (11 per cent) with digitalis intoxication.

Those patients who experienced the clinical syndrome of angina pectoris, coronary artery insufficiency, or previous acute myocardial infarction constituted the coronary artery disease group. Those patients who experienced a recent myocardial infarction in association with complete heart block were placed in the acute myocardial infarction group. Those having myocardial infarction, coronary thrombosis, or significant coronary artery sclerosis at autopsy were also included in these sections. Age alone in the absence of any of these criteria was not deemed sufficient for inclusion in this category. Criteria for the hypertensive heart disease group included a systolic blood pressure of 170 mm. Hg or greater; it is appreciated that this demarcation is an arbitrary one. The diastolic pressure in complete heart block is so variable that it was not employed as a useful criterion. All the cases with rheumatic heart disease had aortic, or mitral, or combined aortic and mitral valve disease with or without a past history of rheumatic fever. The miscellaneous or rare forms of heart disease and those with complete heart block of etiology undetermined are discussed later. Those patients were included in the digitalis intoxication group in whom excessive digitalis appeared to be the cause of the complete heart block. All these patients had heart disease due to one cause or another, but had complete heart block as a consequence of excessive digitalis therapy. This group was regarded as unique and sufficiently different from the other cases to merit separate study. They, therefore, will not be included in the statistical analyses of features such as age, sex, and other factors. This type of heart block is induced by the drug and is not a necessary part of the disease process of complete heart block.

Some of the cases had more than one of the above etiologic features. Those who had hypertension and rheumatic valve disease were classified in the rheumatic group. Patients in whom the heart block developed in relationship to coronary artery disease, i.e., directly with acute myocardial infarction, and those in whom angina or myocardial infarction had been present in the past, were put into the appropriate coronary group even if they had hypertension or rheumatic valvular disease. Although there were 9 instances in this study in which there was a positive serologic reaction for syphilis, in only 2 was syphilitic heart disease present and thought to be related to the complete heart block.

Age and Sex Distribution

Of the 224 cases, 127 (57 per cent) were males and 97 (43 per cent) were females. The age group extended from 10 to 85 years, with 84 per cent occurring in the age group from 41 to 80 years. Table 1 is based upon the age when the patient was first observed by us to have complete heart block and does not necessarily represent the age at which heart block first de-

TABLE 1.—*Age Distribution by Decades*

Age	Number	Per Cent
0–10	1	0.4
11–20	3	1.3
21–30	9	4.0
31–40	6	2.7
41–50	27	12.5
51–60	37	16.4
61–70	76	33.7
71–80	51	22.7
81–90	14	6.3
Total	224	100.0

TABLE 2.—*Age and Sex in Various Groups*

	Total No. Patients	♂	♀	Av. Age yrs.	Age Range yrs.
Coronary artery disease	58	39	19	63.5	40–84
Acute myocardial infarction	49	27	22	62.5	40–85
Hypertensive heart disease	62	33	29	63.4	19–82
Rheumatic heart disease	21	8	13	52.5	16–79
Etiology undetermined	18	9	9	44.5	22–78
Miscellaneous	16	11	5	45.1	10–82
Total	224	127	97	59.3	10–85

veloped or was first observed by others. It should be noted that customarily patients under the age of 12 years are not eligible for admission to the Peter Bent Brigham Hospital.

The average age of all patients when first observed with complete heart block was 58.5 years; if the digitalis group is excluded, the average age was 59.2 years. The 3 groups, i.e., coronary artery disease, acute myocardial infarction, and hypertensive heart disease, were the oldest (62.5 to 63.5 years). The miscellaneous group and the group designated "etiology undetermined" were the youngest, about 45 years, and the group with rheumatic heart disease were intermediate (52.5 years) (table 2).

The average age at death in the 126 cases where the time of death was known was 63.2 years. The corresponding figures for the various subgroups of these cases were as follows: Chronic coronary artery disease, 65.9 years; acute myocardial infarction, 65.2 years; hypertensive heart disease, 60.3 years; rheumatic heart disease, 62.7 years; etiology undetermined, 55.0 years; miscellaneous, 55.0 years. The age was generally a little greater in those who had permanent complete heart block than in those who had transient complete heart block. There was a definite tendency for the males to predominate in all groups except those with rheumatic heart disease, in which group there were 13 females and 8 males.

SYNCOPE

Syncope occurred in 137 cases (61 per cent). It was the first evidence of the illness in 48 cases (21.4 per cent). The frequency of these episodes varied greatly. Rarely, only one such spell of unconsciousness occurred. In others, they may have taken place at daily, weekly, monthly, or sporadic intervals, and there were extreme instances in which actual status epilepticus was present with the effective heart action stopping and starting every few minutes. With the exception of the digitalis intoxication group, syncope occurred in all the subgroups in this study with varying frequency: 77.6 per cent of the chronic coronary artery disease group, 43 per cent of the acute myocardial infarction group, 72 per cent of the hypertensive heart disease group, 38 per cent of the rheumatic heart disease group, 56 per cent of the miscellaneous forms of heart disease, and 44 per cent of the etiology undetermined group.

Descriptions of attacks of syncope vary, and the following serves as an example: "Dizziness comes suddenly without warning and not related to exertion; it begins with a feeling of coldness all over the body, and then a sensation of warmth passes quickly up the body and there is a feeling of fullness and heat in the head; everything becomes black before the eyes and then the feeling passes quickly and a feeling of well being exists thereafter except for a sense of slight oppression in the chest and very slight breathlessness for a few minutes, the whole attack lasting five or ten minutes."

Similarly, as the attacks themselves vary, so might the description vary, but the following are illustrative: "The pulse was 45 and suddenly failed to come through; on auscultation

no sounds were heard for 18 seconds; after cessation of the heart beat, the patient began to quiver, her arms began to twitch and her body began to straighten out, and her face became ashen gray. After the end of the 18 second period, the same heart sounds were heard followed by other heart sounds at irregular intervals, each sound becoming louder but irregularly spaced. About 15 seconds after the end of asystole, the rate increased and then became regular." Another type of observation is illustrated in the following:

> "I was called to see the patient after several so-called minor attacks in quick succession. The patient spoke to me telling me of the shock-like pain traveling over the right arm to the shoulder; while talking to him and feeling the radial pulse, I felt a period of asystole begin, was able to count ten mentally when the patient announced he was having another spell; with stethoscope over the heart no further heart sounds or radial impulses came through for about 25 more counts (thus 35 counts in all); during this time, the patient's face was blanched of all color, eyes were rolled upward, and his hands stiffened; then, the heart began to beat, the patient became flushed, his head came forward, and he spoke almost simultaneously. The patient stated that he remembered nothing and that he did not feel well; there were no twitchings of any sort and the heart rate was beating at a rate of about sixty-four and regular after this attack. In this case asystole of 10 seconds with the patient lying flat in bed caused no symptoms. He was aware that a spell was coming only after that interval of 10 seconds and actual syncope ensued a few seconds later."

There are all degrees of severity of the attacks and there are marked variations in the duration of Adams-Stokes syncope. These range from a brief fleeting aura of faintness to complete unconsciousness, cyanosis, eyes rolled upward, body twitching, face drooping, stertorous breathing, frothing at the mouth, and complete unresponsiveness. With the resumption of the first heart beat there may be sudden awareness of the surroundings and a sense of well being.

The duration of life after the onset of syncope varied greatly among these patients. It was obviously very short in those who had Adams-Stokes attacks for the first time with a fatal acute myocardial infarction. The average duration of life after the first syncopal attack in cases other than those just mentioned was 6.9 years, the range being from several hours to 11 years. In many cases syncope preceded permanently established complete atrioventricular block by a period of months or a few years. Of 39 patients who died in Adams-Stokes attacks, 31 had previous syncope and 8 had no previous syncope. The fact that a patient had previous syncopal attacks with complete heart block would make it seem more likely that he would have a subsequent sudden eventual exitus.

Apart from definite syncope with loss of consciousness, periods of dizziness and weakness were quite common. There were 36 patients (17 per cent) in whom these symptoms occurred without true syncope, 84 (38 per cent) who had both syncope and dizzy spells, and 46 (21 per cent) who had spells of unconsciousness without additional complaints of dizziness.

Palpitation

Palpitation occurred in 43 patients. In comparing the incidence of palpitation with heart rate, it was found that of 55 patients with a slow rate of 30 or less, there were 9 (16 per cent) who had palpitation and 46 who did not have palpitation. Of 169 patients with rates greater than 30 per minute, 42 (25 per cent) had palpitation and 127 did not have palpitation. Although the symptom of palpitation generally connotes a more rapid heart beat, it is significant that the same symptom is not uncommon among those patients who have a very slow heart rate.

The suggestion has been made that in those patients experiencing syncope, the premonitory symptom of palpitation might be useful in predicting syncope due to ventricular acceleration. In this study, 2 of 13 patients with ventricular acceleration (ventricular tachycardia, ventricular fibrillation, ventricular flutter) were aware of palpitation prior to their attack; none of the 21 patients with syncope due to ventricular asystole was aware of palpitation prior to the attack. These cases were all documented by eletcrocardiograms. There were, however, other cases with syncope not documented by electrocardiograms who experienced palpitation but the subsequent rhythm was not ascertained. Only occasionally, therefore, can the symptoms

TABLE 3.—*Heart Rate in Patients with Complete Heart Block*

Heart Rate	No. of Patients
Less than 20	14
21–30	38
31–40	83
41–50	67
51–60	16
61–70	2
71–80	2
81 or above	2
Total	224

of palpitation preceding the syncopal attack aid the physician in distinguishing attacks that are initiated by an accelerated ventricular rate from those that start abruptly with asystole.

CONGESTIVE HEART FAILURE AND DYSPNEA

Objective evidence of congestive heart failure was present in almost 40 per cent of the patients studied. Failure varied from minimal to severe. In 23 patients, heart failure preceded the onset of complete heart block, in 16 congestive heart failure or dyspnea developed concomitantly with the complete heart block, and in 8 these features appeared after the onset of complete heart block. In the other patients, the relationship of the complete heart block to congestive heart failure was not very clear. Only 10 of 85 patients in whom the mode of death was known died of progressive congestive heart heart failure.

Dyspnea was the presenting feature in about one fourth of the cases, and was present clinically in slightly less than two thirds of all the patients. The dyspnea varied from mild to marked, and there did not appear to be any clinical relationship between the heart rate and the degree of dyspnea. Dyspnea and congestive heart failure appeared in patients having a slow heart rate as well as those having a more rapid heart rate. It was noted in a patient with a heart rate of 18 per minute and in another with a heart rate of 72 per minute.

In the therapy of congestive heart failure, all the usual modes of treatment were employed. When needed, digitalis was administered, unless the heart block was due to overdigitalization and continued digitalis would have led to aggravation of the congestive failure.

Congestive heart failure and dyspnea appear to be manifestations of the underlying heart disease, and the presence of complete heart block is incidental in the course of events. Although we have the general impression that the slow heart rate may actually be beneficial to a certain extent and decrease the degree of congestive heart failure, the observations in this study were neither detailed enough nor sufficiently adequate to offer proof in favor of this concept.

HEART RATE

The heart rate varied from a low of 16 to a high of 97, and the over-all average was 38 beats per minute as documented by the electrocardiogram. As shown in table 3, all but 6 patients had heart rates of 60 or less (this does not include the digitalis intoxication group). Rates of 8 and 12 were reported clinically, but not documented by the electrocardiogram. The heart rate was regular in 181 of 224 patients. In the classical description of complete heart block, the rate is usually said to be particularly regular, but there are cases, not too uncommon, in whom the ventricular rhythm is somewhat irregular because of the appearance of ventricular premature beats. It may be mentioned here that there are patients in whom the ventricles as well as the atria are affected by carotid sinus pressure or vagal influence. There were 55 cases of complete heart block having a rate of 30 or less. The average rate recorded in the various groups was as follows: coronary artery disease (nonacute), 32; acute myocardial infarction, 43; hypertensive heart disease, 37; rheumatic heart disease, 45; miscellaneous, 39; etiology undetermined, 43; and digitalis intoxication, 54 beats per minute.

Although the characteristic of complete heart block is a slow, regular rate, slight irregularities were not uncommon, and the actual ventricular rate varied from under 20 to 60 or more. Variability in the heart rate occurred in the same individual at various times.

BLOOD PRESSURE AND PULSE PRESSURE

Systolic blood pressure averaged 172 mm. Hg and diastolic blood pressure averaged 79

TABLE 4.—*Comparison of Blood Pressure and Heart Rate*

	Coronary artery disease	Acute myocardial infarction	Hypertensive heart disease	Rheumatic heart disease	Misc.	Etiology undetermined	Average
Number of cases (224)	58	49	62	21	16	18	
Rate under 40							
Systolic blood pressure	174	169	208	180	154	129	181
Diastolic blood pressure	75	83	90	61	70	69	80
Number cases	46	22	43	9	8	7	135
Average rate	30	31	32	32	32	31	31
Rate above 40							
Systolic blood pressure	189	126	208	142	139	135	156
Diastolic blood pressure	75	70	92	74	68	66	75
Number cases	12	27	19	12	8	11	89
Average rate	44	52	47	54	46	50	49
Over-all Average							
Systolic blood pressure	177	145	208	158	147	132	172
Diastolic blood pressure	75	76	91	68	69	67	79
Number cases	58	49	62	21	16	18	224
Average rate	33	43	36	45	39	43	38

mm. The highest systolic blood pressure was 280 mm. Hg and the lowest systolic blood pressure was 60 mm. The highest diastolic blood pressure was 150 mm. Hg and the lowest was zero. Pulse pressure averaged 93 mm. and ranged from a low of 28 mm. to a high of 180 mm. Hg.

The accompanying table 4 demonstrates the relationship of heart rate to blood pressure and the average of these readings in each subgroup. It is obvious that with well-marked hypertension, the pulse pressure will necessarily be large. In cases without hypertension, however, greater blood pressure readings were more likely to accompany slower heart rates. In following the same individual who goes in and out of complete heart block, it was often found that as the heart rate slowed the systolic pressure rose and the diastolic fell. In that way it was possible for the heart to maintain as great an output, and even a normal one, at the rate of 30 beats per minute as it would with a rate of 70.[7]

HEART SIZE

The heart was considered to be enlarged in 140 of 224 cases. In 52 the enlargement was slight, in 49 moderate, and in 32 marked. The estimate of the increased heart size was based upon x-ray examination or physical findings. Absence of cardiac enlargement in 47 cases of complete heart block was confirmed by fluoroscopic examination or x-ray films. In a patient with rheumatic heart disease and complete heart block, who was followed for a period of over 15 years, cardiac enlargement was never demonstrable. Cardiac enlargement need not necessarily be associated with complete heart block; the degree of heart enlargement for the most part went, pari passu with the accompanying type of heart disease.

OTHER CONDUCTION DEFECTS

Of the 224 patients, there were 62 in whom the electrocardiograms were indicative of right bundle branch block and 60 in whom tracings were of the type generally designated as left bundle branch block. It is evident that in these instances of so-called bundle branch block the impulse may have actually arisen in one of the branches rather than in the common junctional tissue or node. First or second degree block, or both, was present prior to or subsequent to the complete heart block pattern in 67 patients. Two patients had documentary evidence of both right and left bundle

branch block at varying periods while they had complete heart block. Thus, third degree block is frequently preceded by a lesser degree of atrioventricular block and is often accompanied or preceded by bundle branch block.

Other Associated Rhythms

There were 83 patients in whom the atrial rate was under 100 beats per minute. In 41 the rate was between 100 and 120, and in 12 the range was from 120 to 200. There were 2 documented cases of paroxysmal atrial tachycardia with complete heart block. In 57 cases atrial fibrillation was associated with complete heart block, 14 of these patients were in the "digitalis intoxication" group. Atrial flutter concomitant with complete heart block occurred in 4 patients. The atrial rate was fairly constant in some patients with complete heart block and in others the atrial rate varied slightly from day to day. In still others, there were sharp increases in the atrial rate when an abnormal form of atrial rapid heart action developed. The atrial and ventricular rates may simultaneously but independently increase or decrease. In other instances, the atrial and ventricular rates may simultaneously but also independently be altered in opposite directions. Thus, the atrial rate may increase when the ventricular rate decreases or the atrial rate decrease when the ventricular rate increases.

Ventricular tachycardia and ventricular fibrillation were present in 15 cases documented by the electrocardiogram. In some, there followed an appreciable interval of electric inactivity and, in others, the ventricular complexes of complete heart block were quickly resumed after the rapid ventricular rhythm. Ventricular asystole was documented by the electrocardiogram in 21 cases; 10 were in the coronary artery disease group (nonacute), 6 were in the acute myocardial infarction group, 2 in the hypertensive heart disease group, 1 in the rheumatic heart disease group, and 2 in the miscellaneous group.

Observations in this study support the conclusions made by Parkinson, Papp, and Evans,[3] in 1941, that the syncopal attacks may be due to asystole associated with complete heart block or to ventricular acceleration such as ventricular tachycardia or ventricular fibrillation.

Permanence of Complete Heart Block

There were 176 patients with *permanent* complete heart block, 29 others had *transient* complete heart block, and 19 additional patients had repeated transient complete heart block. Those in whom complete heart block was recorded at every examination from its inception to death or to the time of last follow-up were considered to have permanent complete heart block. Included in this group also were those who had transient or intermittent block, or both, but who then progressed to a permanent block of a fixed nature and of long duration. The group with transient complete heart block included those patients who had a single period of complete heart block preceded and followed by a lesser degree of block or normal rhythm. The number of the latter who returned to a normal sinus rhythm was 17 (coronary artery disease, nonacute, 1; acute myocardial infarction, 12; miscellaneous, 1; etiology undetermined, 1; rheumatic heart disease, 1; and hypertensive heart disease, 1). The number of those who returned to partial heart block was 12 (coronary artery disease, nonacute, 2; acute myocardial infarction, 6; hypertensive heart disease, 1; rheumatic heart disease, 1; and miscellaneous, 2) (table 5). Repeated transient block included those patients who had complete heart block on more than one occasion; 7 so classified returned to

Table 5.—*Incidence of Types of Complete Heart Block*

	Permanent block	Transient block	Repeated transient block	Total
Coronary artery disease (nonacute)	52	3	3	58
Acute myocardial infarction	27	18	4	49
Hypertensive heart disease	54	2	6	62
Rheumatic heart disease	17	2	2	21
Miscellaneous	10	3	3	16
Etiology undetermined	16	1	1	18
Total	176	29	19	224

normal sinus rhythm (coronary artery disease, nonacute, 1; acute myocardial infarction, 1; hypertensive heart disease, 2; rheumatic heart disease, 2; and etiology undetermined, 1) and 12 returned to partial heart block (coronary artery disease, nonacute, 2; acute myocardial infarction, 3; hypertensive heart disease, 5; and miscellaneous, 2).

In the majority of patients in this study, complete heart block was of a permanent nature. However, there were some in whom the complete heart block was not permanent but of a transitory nature. In this latter group, it is of interest that the largest number occurred in association with acute myocardial infarction.

Duration of Complete Heart Block

The longest time interval of a patient having complete heart block, documented by the electrocardiogram, was 21 years. The longest duration of complete heart block on a clinical basis was 47 years. There were 4 cases of over 15 years' duration documented by the electrocardiogram, 2 cases of from 20 to 25 years, and 3 from 15 to 19 years' duration on the basis of the clinical picture and history. Aside from those cases in the digitalis group, in which there were some with complete heart block for only a few hours, there were others in whom the duration was less than one day, particularly among those who died of acute coronary thrombosis. In table 6 are recorded the data concerning those cases in whom the diagnosis of permanent complete block was proved by electrocardiogram. The duration of life after the first occurrence of syncope and after the first development of complete heart block, where the time of death was known, varied somewhat in the different subgroups. It was generally about a year longer after the initial syncope (average 35.2 months) than after the first appearance of heart block (aver-

Table 6.—*Comparative Observations of Patients with Complete Heart Block (C.H.B.)*

Group	Age first observed	Length of life after first observed	Age at onset first syncope	Length of life after first syncope	Age onset of C.H.B.	Length of life after onset C.H.B.	Age at death C.H.B.
Acute myocardial infraction (49 cases)	62.4 y. (40y–85y)	11 m. (4h–7y) 34 pts.	63.1 y. (39y–77y) 21 pts.	4 m. (hrs–1y) 14 pts.	62.4 y. (40y–85y) 49 pts.	5.5 m. (hr–5y) 21 pts.	65.2 y 33 pts.
Coronary artery disease nonacute (58 cases)	63.5 y. (40y–84y)	31 m. (1d–18m) 40 pts.	63.0 y. (42y–85y) 42 pts.	39 m. (1d–15y) 28 pts.	63.5 y. (40y–84y) 58 pts.	29.4 m. (1d–18y) 35 pts.	65.9 y. 41 pts.
Hypertensive heart disease (62 cases)	63.4 y. (19y–82y)	28.5 m. (7h–9y) 27 pts.	61.0 y. (42y–82y) 42 pts.	57 m. (15d–11y) 19 pts.	63.1 y. (19y–82y) 62 pts.	29.6 m. (1d–9y) 28 pts.	60.3 y. 29 pts.
Rheumatic heart disease (21 cases)	52.5 y. (16y–79y)	14.5 m. (1d–7y) 11 pts.	56.3 y. (42y–66y) 8 pts.	62.1 m. (1y–8.5y) 5 pts.	52.0 y. (16y–79y) 21 pts.	40.7 m. (12d–7y) 10 pts.	62.7 y. 11 pts.
Etiology undetermined (18 cases)	44.5 y. (22y–78y)	6.4 m. (6d–1y) 5 pts.	40.8 y. (22y–78y) 9 pts.	7.3 m. (1m–13m) 3 pts.	43.5 y. (22y–78y) 18 pts.	5.6 m. (6d–1y) 4 pts.	55.0 y. 5 pts.
Miscellaneous (16 cases)	44.9 y. (12y–82y)	68 m. (5d–24y) 5 pts.	60.3 y. (32y–82y) 10 pts.	16. 2m. (5d–2y) 4 pts.	44.9 y. (10y–82y) 16 pts.	84.8 m. (5d–24y) 4 pts.	55.0 y. 7 pts.
Average (224 cases)	59.2 y.	25.3 m. (4h–24y) 122 pts.	60.2 y. (22y–82y) 132 pts.	35.2 m. (24h–11y) 73 pts.	59.2 y. (10y–85y) 224 pts.	26.2 m. (8h–24y) 104 pts.	63.2 y. 126 pts.

h = hours, d = days, m = months, y = years.

age 26.2 months). When these major groups were compared it was found that the length of life after the first syncope or heart block was greatest in the rheumatic, least in the coronary, and intermediate in the hypertensive group.

Diphtheria

This review throws further light on the concept that was presented over 25 years ago, and which has since been discussed, that diphtheria plays some role in the development of complete heart block.[8] There were 41 (16 per cent) cases in which there was a past history of diphtheria; this seems to us a great deal higher than the incidence in the general population during the time that this group of patients was studied. The exact mechanism is difficult to evaluate, but increased vulnerability to conduction defects apparently exists after infection with diphtheria. A long lapse of time may intervene between the actual infection and occurrence of the complete heart block, perhaps at a time when further stress, insult, or injury is encountered. In regard to diphtheria, it will no doubt play less of a role in the future with decreasing incidence of the infection. However, we would like to emphasize that there is reason to believe that some of the unexplained cases of complete heart block may be due to previous apparently minor infections from which the patient recovers, as a result of which the patient is left more vulnerable, just as occurs after recovery from diphtheria. Among the 18 patients with heart block due to unknown cause, there were 7 who gave a history of previous diphtheria, whereas in all the remaining 206 cases, there were only 33 cases of diphtheria. The distribution of the 41 cases of diphtheria was as follows: coronary artery disease, nonacute group, 13 of 58 patients; acute myocardial infarction group, 2 of 49 patients; hypertensive heart disease group, 11 of 62; rheumatic heart disease group, 4 of 21; miscellaneous group, 3 of 16; etiology undetermined group, 7 of 18; digitalis intoxication group, 1 of 27 patients.

It seems to be more than a matter of coincidence that a past history of diphtheria should be so much more prevalent among those cases in which there is no known cause of heart disease than among those in which definite etiologic factors such as rheumatic heart disease or coronary artery disease are involved. This adds validity to the concept that early diphtheria was related to the subsequent development of heart block.

Serology

There was a total of 9 cases who showed a positive serologic reaction for syphilis. Cases were not considered to have complete heart block on a syphilitic basis unless there was some other evidence of syphilitic heart disease. There were 2 such cases included in the miscellaneous group.

Gallbladder Disease

Because of some suspicion of the relationship between gallbladder disease and Adams-Stokes attacks, its occurrence was investigated. Unfortunately, until very recent years no systematic search for gallbladder disease was made in these cases. Not infrequently, one discovers the presence of gallstones on routine x-ray examination, when there has been very little if any clinical evidence of biliary disease. However, there were 26 patients who demonstrated evidence of cholelithiasis or cholecystitis during the time that they were known to have had complete heart block. Eleven of 58 patients with nonacute coronary artery disease were found to have gallbladder disease as well as 3 of 49 patients in the acute myocardial infarction group, 10 of 62 in the hypertensive heart disease group, 1 of 21 in the rheumatic heart disease group, and 1 of 18 in the etiology undetermined group. Gallbladder disease occurred in no patients in the miscellaneous or digitalis group.

Most instances of gallbladder disease were detected during the past 10 years when interest was aroused concerning the relationship of gallbladder disease and syncopal attacks.[9] In 6 instances a cholecystectomy was performed, and in 4 of these there was striking improvement in the incidence of Adams-Stokes attacks. There was no operative mortality in this small group.

Operative Risk

There were 19 patients who underwent 24 surgical procedures. The following operations were performed with no surgical mortality; cholecystectomy in 6, hysterectomy and salpingo-oophorectomy in 1, spinal fusion in 1, tonsillectomy in 1, thyroidectomy in 2, amputation of toes in 2, anal fistula in 1, hemorrhoidectomy in 1, low-thigh amputation in 1, hernia repair in 1, abdomino-perineal resection for adenocarcinoma of the sigmoid in 1, appendectomy in 1, and multiple pregnancies in 2 patients, one of whom also had an appendectomy and removal of left ovarian cyst subsequent to her pregnancies.

Anesthetics employed in these procedures included ether, nitrous oxide, intravenous Pentothal, spinal anesthesia with procaine, local infiltration with procaine, and field block with xylocaine. It might be pointed out that in the administration of a local anesthetic such as procaine and its derivatives in amounts evoking a systemic effect, a myocardial depressant action might ensue. In general, intravenous procaine is contraindicated in complete heart block.[10]

Two of the patients undergoing cholecystectomy had multiple episodes of asystole during anesthesia and surgery, but with careful observation and management both survived the procedures and are still living.

Complete heart block is not a contraindication for necessary surgical procedures or for pregnancy. It would appear that in anesthesia it is not the anesthetic agent employed during the surgery but the manner and method of administration of this that may determine the success of the procedure.

Follow-up Studies and End Results

Of the 224 patients included in this study, 127 were known to have died, 36 were reported to be living, and 61 did not respond to attempted follow-up. The modes of death in the 127 cases were as follows: sudden death, 39; progressive heart failure, 10; acute coronary occlusion, 22; miscellaneous causes, 18, which included deaths due to uremia, pulmonary infarction, pneumonia, cerebral hemorrhage, and other causes; the actual cause of death was unknown in 38 cases.

One hundred thirty-seven of these cases had syncope and 87 did not. In the former group, 76 were known to have died and in 53 the type of death was also known. Thirty-one deaths occurred suddenly. Among the 87 cases who did not have syncope, 51 were known to have died and the manner of death was known in 36 instances. Only 8 of these died suddenly. It would appear that instant death occurs about 3 times as frequently in those who have syncope as in those who do not. However, sudden death takes place not only because of the conduction defect but also in a manner common to the various types of heart disease.

Coronary Artery Disease

Patients with coronary artery disease constituted the largest of all groups studied (107 cases). Of these, 63 had definite myocardial infarction, about half of which also had clear-cut anginal episodes as well. An additional 44 had angina pectoris without clear-cut evidence of myocardial infarction.

It is of interest that among the cases that were most carefully observed, there were none with anginal manifestations after the development of complete heart block, though many had this symptom before the block appeared. With such a large number of cases having coronary artery disease, it was impressive how rare angina was in those who had a slow ventricular rate.

Males predominated over females, 65 over 42, respectively, as would be expected in any study of coronary artery disease. The age of the patients in this group ranged from 40 to 85 with an average of 64 years.

The various symptoms such as syncope, dyspnea, and palpitation occurred in patients in the coronary artery disease group with about the same frequency as patients in the other groups of the study. The average blood pressure was 176 mm. Hg systolic and 76 mm. Hg diastolic. For the most part, the other clinical features, such as heart rate, heart size, congestive failure, and various arrhythmias, were not significantly different in patients with

coronary artery disease than in patients in the other groups. However, episodes of paroxysmal ventricular acceleration were recorded electrocardiographically in 10 of 107 patients with coronary artery disease in contrast to only 4 of the remaining 117 patients in this study. There was also a difference in the incidence of gallstones in this study (14 in 107 patients in the coronary group, 10 in 62 in the hypertensive group, 2 in the other 55 patients). To be sure, the average age of the coronary and hypertensive heart disease patients was about 10 years greater than that of the others.

Cases of acute coronary thrombosis made up a distinct group with certain peculiar characteristics. Here it is quite clear that the heart block was precipitated by a specific event. In most of the other types of complete heart block, there was no direct cause either for syncopal attacks or for the initial development of the conduction defect, the process being insidious in nature. There was a total of 49 patients with acute myocardial infarction who showed complete heart block. In 2 of these, the block preceded the coronary attack and, in all the others, complete heart block developed during the early days of the acute infarction. It is of interest that heart block occurs about twice as frequently with posterior as with anterior infarctions.

In those cases of acute coronary occlusion in which complete heart block occurred, the immediate mortality was significantly high. Of the 49 cases, 21 died in the brief period of a few days (4 hours to 18 days, average 5.5 days). Of these 21, 6 had had a previous coronary occlusion. Of the 28 who survived the immediate coronary insult, it is of interest that 23 returned to their previous atrial rhythm, 21 to normal sinus rhythm and 2 to atrial fibrillation. Five patients continued in complete heart block; 2 of these had previously had complete heart block, 1 had previously had atrial fibrillation, and the other 2 were undocumented as to their previous rhythm. There was one instance in which the patient had an acute coronary episode with complete heart block and recovered with the return of a normal sinus rhythm. Sometime later he had a second myocardial infarction with a stormy course but survived and maintained a normal sinus rhythm throughout. Of these 28 who survived their acute coronary occlusion, 5 had had a previous similar episode.

It is very impressive that there was not a single instance in which it was known that the patient previously had a normal sinus rhythm and then developed complete heart block with an acute infarction and thereafter continued in complete heart block. This observation corresponds with the general cardiologic experience in thousands of cases of acute coronary thrombosis, for it is extremely rare to see permanent complete heart block result as a direct sequel of an acute attack of myocardial infarction. Permanent complete heart block, as shown in this study, must be an extremely rare immediate sequel of acute myocardial infarction. This is of interest when it is appreciated that about 2.5 per cent of cases of acute myocardial infarction do develop temporary complete heart block.[11]

Another peculiarity of complete heart block occurring with acute myocardial infarction is that the ventricular rate is not infrequently more rapid than is customarily seen in other types of third degree heart block. Whereas the average ventricular rate of all the other cases in this study was 36, the average rate of heart block when it occurs with acute myocardial infarction was 43. Although slow rates of 28 to 35 did occur, there were 8 in which complete atrioventricular dissociation was present with ventricular rates of 50 to 60; in fact there were 2 with ventricular rates over 70, 1 with a rate of 75 and another with a rate of 97. In all these cases there was electrocardiographic confirmation that the atria and ventricles were contracting independently of each other.

Hypertensive Heart Disease

The average age, sex distribution, incidence of syncope and dizziness, dyspnea, and palpitation were not strikingly different in this group of 62 cases with hypertension from the over-all distribution. The pulse pressure average for this group was 117, whereas the average for the remainder was 81. As would be expected because of the classification of these cases, the systolic and diastolic blood pressures were

TABLE 7.—*Miscellaneous Features in Complete Heart Block*

	No. Cases	Rheumatic Fever	Diphtheria	Bundle branch block	Gallbladder disease	Sudden death
Acute coronary occlusion	49	0	2	24	3	6
Coronary artery disease (nonacute)	58	1	13	33	11	16
Hypertensive heart disease	62	1	11	40	10	8
Rheumatic heart disease	21	14	4	5	1	1
Etiology undetermined	18	1	7	7	1	2
Misc. cases	16	3	3	11	0	1
Total	224	20	40	120	26	34

significantly higher. For the most part there were only slight differences in the incidence of other features, some of which are presented in table 7.

Systolic hypertension was a general feature of complete heart block and the diastolic pressure was, as an over-all average, within normal limits. Thus, systolic hypertension might bear some relation to the fact that the average age of all patients studied was 59.3 years. It is not necessary that hypertension be present in every patient having complete heart block. A patient may be quite fit, with a slow heart rate of 30 to 35, and still have the systolic not over 130 mm. Hg. In one patient in this study the systolic pressure was as low as 110 mm. Hg. It is of interest that, in general, there was a fall of systolic and diastolic blood pressure as well as pulse pressure with heart rates over 40. However, in the hypertensive group the heart rate had no effect on the systolic or diastolic pressure levels.

The length of life after the first syncopal attack, in general, was longer in the hypertensive patients than in patients in the coronary artery disease group, and the age at death was about 5 years less than in this latter group.

It would appear that although hypertension is a not infrequent accompaniment of complete heart block, it is not a necessary part of the condition, and, when present, has only a slight effect on the various features and complication of heart block.

RHEUMATIC HEART DISEASE

The average age of patients in the rheumatic heart disease group (21 cases) was 52.5 years, in comparison with an average age of 59.8 years for the other 203 patients. In the 21 patients in this group, 13 were females and 9 were males, which is consistent with the general predominance of rheumatic mitral stenosis in females. Syncope occurred in 39 per cent of the rheumatic patients in contrast to 60 per cent of the remaining groups. Palpitation occurred in 57 per cent as compared with 15 per cent in the remaining 203 patients; atrial fibrillation occurred in 8 of the 21 rheumatic patients (35 per cent) in contrast to only 24 of the 203 patients (12 per cent) in the other groups.

There were differences in the occurrence of some of the clinical features in patients in the rheumatic group as compared with all the others; syncope 39 per cent and 60 per cent, palpitation 57 per cent and 15 per cent, atrial fibrillation 35 per cent and 12 per cent, past history of rheumatic fever 66 per cent and 1 per cent, bundle branch block 54 per cent and 59 per cent. The average ventricular rate in the rheumatic group was 45, while in the others it was 37; the length of life after the onset of syncope was a good deal longer in the rheumatic group, 5.2 years in contrast to 2.8 years. The length of life after the onset of complete heart block was 3.2 years as compared to 2.4 years. The average age at death was 62.7 years while in the others it was 63.2 years.

There were 12 patients with mitral valve disease, 4 with aortic valve disease, and 5 with both. Complete heart block was not common in rheumatic heart disease in general, for there were only 21 such cases out of the many hundreds of valvular cases that formed the background for this study. When it did occur, however, it was a little surprising that mitral stenosis or some involvement of the mitral

valve was present more frequently than aortic valvular disease. It is of interest that complete heart block associated with acute rheumatic myocarditis is rare, none having been observed in this study. A case of transient complete heart block associated with an acute rheumatic flare-up was recently called to our attention.[12]

It is obvious that there should be a much greater frequency of a past history of rheumatic fever and a greater incidence of atrial fibrillation in the rheumatic group than in the others. It is also of interest that the patients with rheumatic heart disease had a higher ventricular rate and lived longer after the onset of syncope than other patients with complete heart block. Although in this study the patients with rheumatic heart disease were younger than those in the other groups, they were still a good deal older than the average patient with rheumatic valvular disease, from which one could infer that heart block in these rheumatic cases required many years for its development.

"Etiology Undetermined"

There were 18 patients with complete heart block in whom no definite etiologic diagnosis could be made. Possible causes that might be invoked were an infection early in life accompanied by a transient myocarditis, a congenital cardiac defect of conduction unknown to the patient or family, trauma to the heart at a previous occasion, a toxic myocarditis, allergic or some other cause, or some specific response of the conduction tissue to noxious agents.

Nine were males and 9 were females. The average age was 44.5 years, the youngest age group. Syncope occurred in 8 of the 18 patients (44 per cent) and in 122 of the 206 remaining patients (59 per cent). Seven of the 18 patients (39 per cent) in this group had diphtheria, whereas the over-all figure was 33 in 206 patients (16 per cent). This makes it very likely that early diphtheria was related to the later development of heart block in some of these cases.

It is of interest that in this group without coronary artery disease, valvular disease, or hypertension, the average blood pressure was 132/67 mm. Hg (pulse pressure of 65) whereas the average blood pressure in the others was 171/78 mm. Hg (pulse pressure of 93). Thus it is pertinent to point out again that hypertensive levels are not a necessary concomitant part of complete heart block. Alteration of heart rates below and above 40 beats per minute had very little effect on comparative systolic and diastolic blood pressures. Atrial fibrillation was present in 4 of the 18 patients.

The age at onset of syncope, the age at onset of complete heart block, and the duration of life after the development of complete heart block in the two groups, namely those with etiology undetermined and all others in this study, were as follows: 40.8 years and 61.5 years, 53.5 years and 60.6 years, and 5.6 months (4 patients) and 27 months (100 patients), respectively. The average age of death was 55.0 years (5 patients) as compared with 63.5 years (121 patients). The youngest patient in this entire study having syncope was 22 years of age and was among this subgroup "etiology undetermined."

This group obviously contained cases of complete heart block without major organic cardiac defects, such as valvular or coronary artery disease. Here the heart block appears in a purer form. It is of interest that such cases may be normotensive, are younger, and have slightly higher ventricular rates. The greater incidence of a past history of diphtheria is also of significance and lends interest to the concept that an early infection may be conducive to the later development of complete heart block. Finally, it is our distinct impression that patients in this group have a better prognosis as far as the duration of life is concerned. Although there were only 4 cases that were known to have died after an average interval of only 5.6 months after the first onset of complete heart block, there are at least 3 others who are still alive and well 15, 10, and 9 years after the complete heart block was first observed.

Miscellaneous Cases

There were 16 patients in this study in which there were unusual types of heart disease associated with complete heart block. For purposes of description we have further sub-

divided this group into those (a) with complete heart block produced by pressure on the carotid sinus, (b) with complete heart block due to syphilitic heart disease, and (c) other cases with rare etiologic causes of complete heart block.

Carotid Sinus Group. There were 6 cases in this group. These six did not have complete heart block prior to carotid sinus stimulation. Two had normal sinus rhythm and 4 had second degree atrioventricular block. Both of the first 2 and 2 of the latter 4 had ventricular asystole during carotid sinus stimulation at a time when the atria were contracting though a little more slowly than before. In all instances the rhythm returned to the state that preceded the carotid sinus test. Two of the cases that showed partial block manifested transient complete atrioventricular dissociation during the test. A follow-up observation in these 6 cases revealed that 2 subsequently had transient complete heart block, 2 developed permanent complete heart block, and 1 still showed the same partial heart block that was previously present 4 years later; in 1 the subsequent course was not ascertained.

One of the 6 cases presented some interesting features. This patient was a physician 46 years of age. He had had previous syncope and also complained of dizziness. During carotid sinus stimulation ventricular asystole occurred and the atrial rate was little disturbed; he also had similar spontaneous episodes with the return to normal sinus rhythm. At other times he developed brief episodes of spontaneous complete atrioventricular dissociation. During this time following a brief exercise test the atrial rate would accelerate and independent ventricular rhythm would result temporarily; as the atrial rate returned to the pre-exercise level, normal sinus rhythm would return. Finally, two years later, permanent stable complete heart block developed and has persisted for some years. He is at present quite fit and carrying on an active practice.

It would appear that in patients who have had syncope, if carotid sinus stimulation results in temporary ventricular asystole with continuation of atrial activity or in transient complete atrioventricular dissociation, the subsequent development of complete heart block is likely to occur.

Syphilitic Heart Disease. There were only 2 cases of complete heart block in this group. Both were males and both had syncope, enlarged hearts, and bundle branch block. One had a blood pressure of 205/50 and had congestive heart failure, with a ventricular rate of 51 beats per minute. The other had a blood pressure of 140/55 and a heart rate of 20 but did not have congestive heart failure. Postmortem examination of the former patient showed a gumma in the region of the septum. Inasmuch as syphilitic heart disease in general is becoming increasingly infrequent, this unusual form of heart block is likely to become extremely rare in the future.

Rare Etiologic Causes of Complete Heart Block. Because of the peculiar nature of each of these cases, a brief description follows:

Case Reports

Case 1. J.A., a 21 year old man who, after having an infection of the foot, developed partial block and then permanent complete heart block; he had no syncope. He showed a blood pressure of 115/60, a heart rate of 32, and left bundle branch block. He lived for 24 years after the onset of complete heart block. Inasmuch as there are rare instances of localized pyogenic abscesses in the heart muscle, it is not unlikely that such an infection occurred in this case, which healed and resulted in a permanent complete heart block.

Case 2. L.S., a 28 year old man who had been told that he had a slow heart during an attack of diphtheria as a child; it was not known what his rate was during the remaining years of childhood but from the ages of 18 to 28 he knew that his heart was slow. When examined at the age of 28 he had complete heart block and a ventricular rate of 44; the blood pressure was 115/60. He had never had syncope. The relationship of diphtheria and complete heart block has been discussed in greater detail earlier in this paper.

Case 3. J.V., an 82 year old man, was a patient who had syncope three weeks prior to admission. His blood pressure was 160/90 and the heart rate was 37. He had a calcified mitral annulus by x-ray examination. Such calcification as a concomitant of heart block is probably not infrequent.[13]

Case 4. J.D., a 12 year old boy, was a patient in whom heart block had been noted at the age of two weeks and had subsequent heart rates varying from 53 to 135 during the 12 years prior to entry. He had

a murmur suggestive of ventricular septal defect. His blood pressure was 125/75 and the heart rate when last seen was 47. He has had no syncope. He is now 33 years old and employed as a laborer. This probably is an instance of congenital heart block.

Case 5. R.K., a 10 year old boy, was a patient who was born with a slow heart and a "leaky valve," had pneumonia two weeks prior to admission, and had an irregular pulse with the rate of 21; the first heart sound varied in intensity. Years later he had a cerebral episode at the age of 27 with a heart rate reported as 45 beats per minute. This is another instance of congenital heart block.

Case 6. M.C., a 28 year old woman, had had no syncope but had had renal shutdown after trauma and hematuria followed by bilateral staghorn calculi. She developed oliguria with no benefit from nephrostomy, and later had uremia. She developed complete heart block during the last six days of life. Postmortem findings included deposits of calcium crystals in the myocardium. One may speculate that the calcium deposits in the heart muscle may have impaired conduction in the A-V node or bundle of His.

Case 7. C.R., a 50 year old man, for three weeks prior to admission had had a chest cold, lassitude, generalized aching, chills, fever, and night sweats. Three days after admission he developed complete heart block and syncope and died 11 days later. Postmortem findings revealed vegetations in the right ventricle and a necrotic cavity in the interventricular septum extending to the bundle of His.

Case 8. H.T., a 35 year old man, had experienced blurred vision and syncope four years prior to admission and for two months prior to admission had had recurrent syncope. This patient had a precordial systolic murmur and was regarded as having probable congenital interventricular septal defect.

A review of the above 8 cases would indicate that complete heart block may result on rare occasions from a variety of causes. Unusual mechanisms should therefore be sought for in any case of complete heart block where the more common causes, such as hypertensive heart disease, valvular disease, or coronary artery disease, are lacking.

Digitalis Intoxication

In addition to nausea, vomiting, and yellow vision, it is well known that cardiac arrhythmias are manifestations of overdosage of digitalis and its glycosides. In this study there were 27 cases of complete heart block due to digitalis. There were 15 males and 12 females; the average age of patients in this group was 52 years with a range of 13 years to 80 years. Those in the digitalis group represent 11 per cent of all patients in this study. Two patients had hypertensive heart disease, 4 had myocarditis of undetermined cause, and of the 21 remaining, 17 had rheumatic valvular disease and 4 had a history of rheumatic fever without valvular disease. In the 27 patients placed in this group, there was an obvious relation between digitalis administration and complete heart block. Therefore, the block was of a transient or intermittent type in 17 of the 21 patients in this group who died with complete heart block. Features such as palpitation, blood pressure (the average was 148/78), heart size, and partial heart block were no different in this group than in the others. It was of interest that syncope did not occur in any patient during the period of complete heart block due to digitalis intoxication. This is unusual in that syncope occurred in 137 (61 per cent) of the other 224 cases and was about equally frequent in each of the various groups. The heart rate was higher in this group (54 beats per minute) than in any other group (over-all average 38 beats per minute). The range of the heart rate was 32 to 98 beats per minute. Atrial fibrillation was present in 17 patients (63 per cent) in contrast to 43 of the other 224 patients (19 per cent). This would be expected because of the nature of the cases making up this group. Other arrhythmias were present prior to the development of complete block. Ventricular premature beats were recorded in only 4 cases and transient ventricular fibrillation in 1 case. Bundle branch block was noted in 4 of the 27 cases (15 per cent) but occurred in 122 of the other 224 cases (55 per cent). All the patients in this group received digitalis because of congestive heart failure. Five patients had received intravenous strophanthin during hospital admissions prior to 1920.

In general, it can be stated that excessive doses of digitalis are occasional causes of complete heart block. One can add that it is a very *rare* occurrence considering the fact that so few of the thousands of cardiac patients who received digitalis therapy in this hospital developed complete heart block. The impression

is gained that this complication arises in very sick patients who are not responding to medication, and in whom one is tempted to push the drug in a last hope of improving the circulation. In these patients with complete heart block the ventricular rate is apt to be more rapid than in other patients with complete heart block and syncope is extremely rare. The block will disappear when the drug is discontinued provided the patient survives. This group differs from some of the other groups in that bundle branch block is less common and a past history of diphtheria is very rare (1 out of 27).

Treatment

Before embarking on the therapy for complete heart block, one naturally would prefer to have the diagnosis well established. Actual recognition of complete heart block, if it persists, is a fairly simple matter. A more difficult problem is presented when patients have fainting spells of short duration, but when seen by the physician, show little or no evidence of conduction defect. They may then be readily confused with, or actually misdiagnosed as, cases of hysteria, major or minor epilepsy, or other disease entities. Occasionally no satisfactory diagnosis can be made until the case is carefully observed during an actual spell.

Treatment of complete heart block consists of two parts. The first and generally the most urgent is the treatment, immediate or preventive, of the syncopal attacks. The second is the treatment or the management of the more static slow heart rate that generally accompanies this condition. When syncopal attacks come rarely, i.e., at intervals of many months or years, it is obviously difficult to outline a program of therapy to prevent recurrences. One will have to administer a specific medication or other mode of therapy daily and constantly for a very long time before one can be convinced that attacks are being prevented. However, if the attacks recur frequently, every few minutes, hours, or days, one can quickly determine whether or not any given procedure is effective. One can readily see, therefore, that under certain circumstances heroic measures might be needed when syncopal seizures appear to be imminent and critical, while at other times no constant therapy might be indicated.

A further therapeutic consideration is the set of circumstances under which heart block with or without periods of asystole may arise. The therapy of a case of Adams-Stokes disease occurring acutely in the midst of an attack of acute myocardial infarction with accompanying prolonged shock may demand one method of treatment while similar asystole coming as an isolated event in a patient with well compensated hypertensive heart disease, or with no other important cardiac disability, might demand an entirely different therapeutic approach.

Before undertaking the type of therapy for an attack of syncope, it would be very helpful if we could establish the exact physiologic nature of the episode. As has been discussed before, in general, there are two possible mechanisms involved: (1) a sudden ventricular arrest not preceded by any ventricular irritability and (2) a condition in which the initial events are ventricular extrasystoles or ventricular tachycardia ending in ventricular flutter or fibrillation. Electric inactivity with the arrest of the heart in cases showing the latter disturbance may take place after a few premature beats or after a more lengthy interval of ventricular irritability and acceleration. It is generally impossible to distinguish one type from the other because electrocardiograms are rarely available the moment these sudden events occur. However, one may suspect that ventricular acceleration precipitates attacks if it is possible to obtain evidence that ventricular extrasystoles or tachycardia have been occurring during the intervals between major episodes. Likewise, the detection of short pauses without ventricular acceleration at different times would favor the first of the two mechanisms as a cause.

Therapy for the Acute Attack. Sympathomimetic amines have been regarded as having the most potent effect on the rhythmic function of the heart.[14] In complete heart block our attention is focused on the fundamental properties of the heart, particularly those of rhythm and conduction. Sympathomimetic amines such as epinephrine, n-isopropyl-

norepinephrine (Isuprel), and ephedrine appear to have the effect of stimulating the rhythmic function of the heart. Other sympathomimetic amines such as Neosynephrine, norepinephrine, methoxamine (Vasoxyl), and Wyamine have little or no effect on increasing the rhythmic function of the human heart and, therefore, serve little or no purpose in increasing the heart rate in complete heart block.

For the acute attack of asystole when heroic measures are indicated, epinephrine 0.3 ml. to 0.5 ml. of 1:1000 aqueous solution should be administered by intracardiac injection if the circulation has ceased; this is imperative as standstill affords no means of transportation of the medication to the coronary arteries and thence to the rhythmic foci of the heart itself. If the peripheral circulation is effective, then the epinephrine can be administered parenterally. This may be repeated at frequent intervals as the apparent duration of the accelerating effect is about 8 to 15 minutes. Constant intravenous drip may also be effectively employed. Subcutaneous doses of 0.5 ml. of 1:1000 aqueous solution or 0.5 to 1.0 ml. of 1:500 epinephrine in oil solution intramuscularly are also effective. The time interval of administration is dependent upon the degree of responsiveness; one patient may require an injection every two hours while another patient may require an injection every hour.

More recently isoproterenol (isopropylnorepinephrine, Isuprel) has been introduced and found to be effective in increasing the rhythmic function of the heart.[15, 16] This may be administered in doses of 0.02 mg. intravenously or by intracardiac injection. It may be repeated every 10 to 15 minutes. The subcutaneous dose is 0.2 mg. every 40 to 60 minutes. A constant intravenous infusion at the rate of 2 to 6 μg./min. has been administered. Constant attention must be given to the cardiac mechanism as the infusion should be titered to the desired heart rate and should be discontinued if the patient unblocks and the normally conducted impulse is initiated.

On recent theoretic grounds it is possible that adrenal steroids may be of value in heart block. The rationale for such therapy is based on the following observations.[19] In a group of 50 patients with Addison's disease the mean P-R interval measured 0.18 second, and 20 per cent exhibited heart block during some phase of their disease. In a group of 34 patients with Cushing's syndrome, the mean P-R interval duration was 0.14 second and A-V conduction was consistently shortened when the underlying disease was adrenal hyperplasia. The abbreviation of the P-R interval appeared to correlate with the urinary 17-ketosteroid excretion. Administration of cortisone to patients with Addison's disease and resection of the hyperplastic adrenal gland in patients with Cushing's syndrome respectively shortened and lengthened the P-R interval. When cortisone is given to patients without endocrine disorders, there is likewise a decrease in this interval. It may be that adrenal steroids participate in facilitating A-V conduction.

In the acute attack, irritation of the heart with a direct needle prick may stimulate systole. The external pacemaker may also serve a useful purpose[17] and direct massage of the heart can be a lifesaving procedure. Recently, sodium lactate intravenously has been suggested as useful in therapy.[18]

In patients having Adams-Stokes attacks associated with acute myocardial infarction, the shock state is an added threat. The practical importance of maintaining a pacemaker as well as the peripheral circulation is obvious. Theoretic considerations and data accumulated thus far would lend support to the belief that the cardiogenic factor rather than the peripheral vascular factor is the important feature of preventing the shock state. Intravenous isoproterenol not only increases the rhythmic function but also increases the peripheral systolic and diastolic blood pressures, if shock has been previously present.

If the acute attack is identified as ventricular acceleration it would seem that certain cardiac depressants might be preferred, but the effects are not altogether clear. It is a common experience that in patients who have ventricular tachycardia or ventricular fibrillation but do not have complete heart block, procaine amide and quinidine can be beneficial and epinephrine harmful. But the situation is not so simple when the patient has complete heart block. Here the

same sequence of events does not prevail as when complete heart block is not present, and it would seem that procaine amide, quinidine, and possibly potassium should not be used.[10, 20]

If the acute attacks occur and one is unable to identify their mechanism, the recommended course to be followed is one in which asystole is assumed to be the underlying cause.

Therapy for Prevention of Subsequent Attacks. The administration of therapeutic agents will depend upon the frequency of the attacks. If the attacks are rare and very infrequent, perhaps no therapy is indicated. However, if they are frequent, sublingual isoproterenol in doses of 15 to 30 mg. every four hours or ephedrine sulfate, 25 to 50 mg. 4 times daily may be of value. Occasionally barium chloride, 30 mg. in 4.0 ml. solution 4 times daily, will be found useful. Aqueous epinephrine, 1:100 as a nebulizer spray; epinephrine in oil, 1:500 intramuscularly once or twice daily; isoproterenol, 1:200 as a nebulizer spray, or atropine in isolated circumstances may all be measures worthy of trial. When the heart rate is slow, 18 to 22 beats per minute, and the patient is in a semistupor, any possible means of increasing the rate should be employed.

Thyroid gland has been recommended for complete heart block, but its value is uncertain. Ammonium chloride by its acidifying effect may theoretically be beneficial. In 1 patient who had syncopal attacks in which the heart would stop regularly on holding a deep inspiration, the condition was immediately controlled on large doses of ammonium chloride. This patient also had occasional spontaneous attacks that did not appear to be related to respiration. In this series, one patient received 20 mg. of corticotrophin over a 12 hour period intravenously and the heart rate decreased, the patient appeared critical, pale, moist, and weak. More complete evaluation of the role and effect of adrenal steroids is necessary. We believe strychnine, Metrazol, picrotoxin, Coramine, and caffeine are of little or no value in the treatment of Adams-Stokes disease. (If complete heart block is a result of quinidine therapy, however, caffeine, oxygen, and artificial respiration would be indicated.)

An attempt was made to evaluate the role of cardiac depressants such as quinidine, Pronestyl (procaine amide), and potassium in ventricular acceleration—ventricular tachycardia, ventricular flutter, ventricular fibrillation. It has been thought that these compounds might be of value in Adams-Stokes attacks when these abnormal ventricular rhythms are present. These drugs suppress the rhythmic function of the heart but prolong conduction and suppress myocardial contractility. Paradoxically, the administration of procaine amide and quinidine may actually result in the production of ventricular accelerated rhythms when given to patients with complete heart block. Although it is not simple and clear-cut, these drugs should probably not be employed at any time if complete heart block is present.

In those patients who have complete heart block and in whom congestive heart failure develops, digitalis therapy should be employed with somewhat more careful supervision. Other usual treatment for decompensation such as ammonium chloride, aminophyllin, and diuretics should be used as necessary. It is not altogether clear whether digitalis has a beneficial effect in those patients who do not have objective signs of failure. It is controversial whether there is any value in trying to slow the atrial rate so as to enhance a 2:1 partial block in patients having complete heart block.

Discussion

There is some vagueness concerning the definition of Adams-Stokes disease. By some it is confined only to those who have a slow ventricular rate, the atria beating independently and more rapidly, and who are also subject to attacks of syncope. Others would include patients with syncopal attacks who display periods of asystole but at other times do not show atrioventricular dissociation. Heart block of varying degree may be present in such cases during the short periods of the major episodes, but with recovery, little evidence of conduction defect such as P-R interval of 0.22 second or incomplete bundle branch block, may remain. In this present review we have included all cases that had complete atrioventricular dissociation with an independent ventricular rate slower than the atrial whether the atria

were contracting or fibrillating, and also whether or not there had been syncopal attacks.

It is evident that complete heart block occurs in a great variety of conditions; in the young and in the old, with valvular or nonvalvular disease, with or without hypertension, in a transient or permanent form, as a direct result of excessive digitalis administration, or as a consequence of a great variety of etiologic causes. The most common cause is coronary artery disease with resultant myocardial fibrosis. There is reason to believe that some otherwise benign infections, from which patients apparently make a complete recovery, can be responsible for the development of heart block many years later in some instances. In such cases a transient myocarditis may have involved the conduction apparatus, only to manifest its dire consequences many years later. Among these early infections diphtheria formerly was a prominent one. Many other simple infections such as measles, mumps, scrub typhus, undulant fever, infectious mononucleosis, poliomyelitis, and others may also be in this category. It is difficult to have pathologic proof of this because these patients obviously recover from the early infection. Indirect evidence to support this view would be afforded if some of these rare cases of transient conduction defects occurring in benign infections were followed and years later found to have heart block. We know of no such fortuitous recorded cases. An example of a well-documented fatal form of myocarditis of undetermined origin that did manifest complete heart block with syncopal attacks has been published.[21] If such a case had recovered and eventually developed Adams-Stokes attacks, this would have been proof of the above concept.

The clinical picture presented by patients with complete heart block also varies greatly from case to case. There are instances where syncope never occurs and the patient feels fit and able to carry on normal or even strenuous activities. In others, syncopal attacks may be frequent, occasionally presenting the picture of status epilepticus. It is obvious that heroic therapeutic measures might be necessary under the latter circumstances, whereas with the former no medication whatever would be needed for years at a time.

The actual cause for ventricular arrest or acceleration remains a mystery. The structural disease that is present in these patients is for the most part unalterable, except in acute cases such as those with acute myocardial infarction. The accompanying heart disease is the same before, during, and after the actual syncope. What, therefore, could be the trigger mechanism that produces the asystole and what is the mechanism that restores the heart beat? The two factors that can act instantaneously are neurogenic or changes in the caliber of vessels, or both. A nerve reflex may suddenly prevent or augment the formation of impulses. A sudden constriction in the caliber of the minute arteriole supplying the conduction tissue can conceivably produce an arrest of the heart. With these mechanisms, the chemical state of the involved tissue may be sufficiently altered to impair its function. Furthermore, the process must be reversible as the attacks so often cease spontaneously. Is there some chemical substance that is released within the body or accumulates in the involved tissue that finally reverses the deleterious process that is going on? These are questions that at present are unanswered.

As is true in many aspects of heart disease, some of the events that occur in heart block are entirely unpredictable. This is particularly true of the attacks of faintness and actual syncope. Some cases of complete block need the customary treatment for congestive failure; others are completely free of congestive symptoms and remain so indefinitely and therefore require no such treatment. In the main, therapy is directed at the actual attacks of syncope.

Summary

A review was made of 251 cases of complete heart block. These were divided into the following groups: coronary artery disease (nonacute), 58 cases; myocardial infarction (acute), 49 cases; hypertensive heart disease, 62 cases; rheumatic heart disease, 21 cases; "etiology undetermined," 18 cases; miscellaneous, 16 cases; and digitalis intoxication, 27 cases. The

main analysis concerned the 224 cases not related to digitalis.

Of the 224 cases, 127 (57 per cent) were males and 97 (43 per cent) were females. The age when first observed by us varied from 10 to 85 years (average 59.2 years) with 84 per cent occurring between 41 and 80 years. The youngest group was the one designated "etiology undetermined." The average age at death in 126 fatal cases was 63.2 years.

Syncope occurred in 137 cases (61 per cent). There were no instances of syncope in the "digitalis group." The average duration of life after the first syncopal attack, excluding those who died of acute myocardial infarction, was 6.9 years (range, several hours to 11 years). In many instances syncope preceded complete heart block by a few months to a few years.

Palpitation was a definite symptom in 43 cases. It was a little more common in those with a more rapid ventricular rate. Only occasionally was this symptom helpful in deciding whether attacks of syncope were initiated by ventricular acceleration.

Congestive heart failure was present in about 40 per cent of the cases. This could precede, accompany, or follow the onset of complete heart block. On the other hand, anginal pain was extremely rare during established complete block with slow ventricular rates.

The ventricular rate during complete heart block varied from 16 to 97 (average 38). Six patients had rates over 60 (excluding the digitalis group). Although the ventricular rate is generally regular, in many patients slight irregularities were present.

Although cardiac enlargement of some degree was found in 140 of 224 cases, there were 47 in which no enlargement was detected by x-ray examination. In one instance known to have had complete heart block for 15 years, cardiac enlargement was never demonstrable.

Bundle branch block was noted in 122 cases, 62 of the left and 60 of the right type. First or second degree atrioventricular block was present before or after complete heart block in 67 instances. In 57 cases atrial fibrillation was present, 14 of these were in the "digitalis intoxication" group. Ventricular tachycardia or ventricular fibrillation, either transient or terminal, was observed in 15 cases.

In 176 cases the block was permanent, in 29 it was transient, and in 19 there were repeated bouts of transient complete block. Single episodes were most common in the group of acute myocardial infarction.

The longest duration of heart block proved by electrocardiogram was 21 years, although one patient was known, on clinical examination, to have had a block for 47 years. The average duration of life after the first syncopal attack, including those who died within a few days of acute myocardial infarction, was 35.2 months, and after the first appearance of complete heart block it was 26.2 months.

As to etiologic causes, statistical evidence was presented to support the view that early diphtheria was related in some cases to latent heart block. Syphilis was a cause in only two instances. There was reason to believe that minor infections early in life might well have been the cause in some cases. In the majority of instances, disease of the coronary arteries was the main cause.

Gallbladder disease, generally with stones, was a frequent finding, and cholecystectomy appeared to alter the condition favorably. Nineteen patients underwent 24 major surgical operations without any operative mortality.

One hundred twenty-seven of these cases were known to have died. The mode of death was known in 89 instances. Sudden death occurred in 39 instances and was about three times as common in those who had had syncope than in those who had not.

Of particular interest was the group who had complete heart block during acute myocardial infarction. The immediate mortality was high, 21 of 49 cases. In all those who survived, the rhythm returned to the one which prevailed before the myocardial infarction. Another peculiarity was the ventricular rate in this group; often it was more rapid than is customarily seen in complete block.

The hypertensive group was large (62 cases). Hypertension was also present in many of the cases classified in the other groups, particularly those with coronary artery disease. However,

an elevated blood pressure was by no means a necessary accompaniment of complete heart block.

There were only 21 cases of rheumatic heart disease; 12 had mitral valve disease, 4 had aortic valve disease, and 5 had both. It is clear that complete heart block is an uncommon complication of rheumatic valvular disease.

There were 18 cases with "etiology undetermined." In these, some otherwise innocent infection early in life might have been the cause. In general, patients in this classification had a better prognosis.

There were 16 cases that made up the miscellaneous group. In these cases sensitive carotid sinus, syphilitic infection, and other interesting and peculiar factors such as an infected foot, calcium deposits in the heart associated with uremia, and congenital heart disease, formed the background for the heart block.

Digitalis intoxication was a direct cause of complete heart block in 27 instances. Here the condition was transient or terminal. Syncope did not occur in this group, and the ventricular rate was somewhat higher than in the other cases.

Various methods of treatment both for the acute episode and for the prevention of recurrences were analyzed. Therapeutic agents which increase the rhythmic property of the heart, such as epinephrine, isoproterenol, ephedrine, and a mechanical cardiac pacemaker were found to be useful.

Summario in Interlingua

Esseva facite un revista de 251 casos de complete bloco cardiac. Le serie total esseva dividite in le sequente gruppos: 58 casos (non-acute) de morbo de arteria coronari, 49 casos (acute) de infarcimento myocardial, 62 casos de morbo cardiac hypertensive, 21 casos de morbo cardiac rheumatic, 18 casos a "etiologia indeterminate," 16 casos miscellanee, e 27 casos de intoxication a digitalis. Le analyse principal se restringeva al 224 casos non relationate a digitalis.

Le 224 casos includeva 127 masculos (57 pro cento) e 97 femininas (43 pro cento). Le etate del patientes quando illes esseva primo observate per nos variava ab 10 a 85 annos. Le etate median esseva 59,2 annos, e 84 pro cento del patientes habeva inter 41 e 80 annos. Le gruppo le plus juvene esseva le casos a etiologia indeterminate. Le etate median al tempore del morte in le 126 casos mortal esseva 63,2 annos.

Syncopes occurreva in 137 casos (61 pro cento). Nulle caso de syncope occurreva in le gruppo a digitalis. Le duration median del superviventia post le prime attacco syncopic (non includente patientes qui moriva ab acute infarcimento myocardial) esseva 6,9 annos, con limites minimo-maximal de alicun horas e 11 annos. In le majoritate del casos, syncope precedeva complete bloco cardiac per un periodo de inter alicun menses e alicun annos.

Palpitation esseva un symptoma definitive in 43 casos. Illo esseva alique plus frequente in patientes con augmentate frequentias ventricular. Iste symptoma adjutava nos solmente in rar casos a decider si attaccos de syncope esseva initiate per acceleration ventricular.

Congestive disfallimento cardiac esseva presente in circa 40 pro cento del casos. Isto poteva preceder, accompaniar, o sequer le declaration del complete bloco cardiac. Del altere latere, dolor anginal esseva extrememente rar durante establite bloco complete con reducite frequentia ventricular.

Le frequentia ventricular durante complete bloco cardiac variava ab 16 a 97 (con un valor median de 38). Sex patientes habeva frequentias de plus que 60 (non includente le gruppo a digitalis). Ben que le frequentia ventricular es generalmente regular, in multe patientes il occurreva leve irregularitates.

Ben que allargamento cardiac esseva constatate in 140 ex 224 casos, il habeva 47 casos in que nulle allergamento cardiac esseva detegite per le examine roentgenologic. In un patiente con complete bloco cardiac de un duration confirmate de 15 annos, nulle allargamento cardiac esseva unquam demonstrabile.

Bloco de branca esseva notate in 122 casos, de branca sinistre in 62 e de branca dextere in 60 casos. Bloco atrio-ventricular del prime o secunde grado esseva presente ante o post complete bloco cardiac in 67 casos. In 57 casos il habeva fibrillation atrial. Dece-quatro de iste casos pertineva al gruppo de patientes con

'intoxication a digitalis." Tachycardia ventri-ular o fibrillation ventricular, transiente o erminal, esseva observate in 15 casos.

In 176 casos le bloco esseva permanente. In 29 illo esseva transiente. E in 19 casos il habeva repetite episodios de transiente bloco complete. Episodios unic esseva le plus frequente in le gruppo de acute infarcimentos myocardial.

Le plus extense duration de bloco cardiac, electrocardiographicamente demonstrate, esseva 21 annos, sed in un patiente evidentia clinic esseva disponibile que indicava bloco cardiac de un duration de 47 annos. Le superviventia median post le prime attacco syncopic (includente le patientes qui moriva intra alicun dies in consequentia de infarcimento myocardial) esseva 35,2 menses; post le prime manifestation de complete bloco cardiac, illo esseva 26,2 menses.

Quanto al question etiologic, nos ha presentate datos in supporto del conclusion que le precoce occurrentia de diphtheria esseva relationate in certe casos con le disveloppamento de un latente bloco cardiac. Syphilis esseva le causa in solmente duo casos. In un serie de casos il habeva justificationes a vider le causa in minor infectiones in juvene annos del vita. In le majoritate del casos morbo del arterias coronari esseva le causa principal.

Morbo del vesica biliari, generalmente con calculos, esseva un observation frequente, e cholecystectomia pareva influentiar le condition favorabilemente. Dece-nove patientes esseva subjicite a 24 major operationes chirurgic sin ulle mortalitate operatori.

In 127 casos il esseva cognoscite que le patientes esseva morte. Le modo del morte esseva cognoscite in 89 casos. Mortes subitanee esseva characteristic de 39 casos; illos esseva circa tres vices plus commun in patientes con syncope que in patientes qui non habeva habite syncopes.

De interesse special esseva le gruppo de patientes qui habeva complete bloco cardiac durante acute infarcimento myocardial. Le mortalitate immediate esseva alte: 21 inter 49 casos. In omne le superviventes le rhythmo retornava al forma prevalente ante le infarcimento myocardial. Un altere peculiaritate in iste gruppo esseva le frequentia ventricular: frequentemente illo esseva plus alte que lo que es commun in casos de bloco complete.

Le gruppo hypertensive esseva grande. Illo includeva 62 casos. Hypertension esseva etiam presente in multes del casos classificate in le altere gruppos, specialmente in le gruppo de morbo del arterias coronari. Tamen, elevation del pression sanguinee esseva non del toto un accompaniamento necessari de complete bloco cardiac.

Il habeva solmente 21 casos de rheumatic morbo cardiac: 12 con morbo de valvula mitral, 4 con morbo de valvula aortic, 5 con ambes. Il es clar que complete bloco cardiac es un complication non commun de rheumatic morbo valvular.

In 18 casos le etiologia esseva "indeterminate." In illos un alteremente innocue infection durante epocas precoce del vita esseva possibilemente le causa. In general, patientes in iste gruppo habeva un melior prognose.

Le gruppo miscellanee consisteva de 16 casos. In iste casos le bloco cardiac esseva associate con sensibile sinus carotide, infection syphilitic, e altere interessante e specialisate factores, como per exemplo infection del pede, depositos de calcium in le corde in combination con uremia, e congenite morbo cardiac.

Intoxication a digitalis esseva le causa directe de complete bloco cardiac in 27 casos. In illos le conditiòn esseva transiente o terminal. Syncope non occurreva in iste gruppo, e le frequentia ventricular esseva alique plus alte que in le altere casos.

Es analysate varie methodos de tractamento, tanto pro le episodio acute como etiam pro le prevention de recurrentias. Agentes therapeutic que augmenta le rhythmicitate del corde (p.ex. epinephrina, isoproterenol, e ephedrina) e le uso de un mechanic pacemaker cardiac se monstrava utile.

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The Hemodynamic Results of Surgical Correction of Atrial Septal Defects:

A Report of Thirty-three Cases

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An experience with surgical treatment for atrial septal defects in 59 patients has given evidence as to the safety and efficacy of the procedure utilizing the atrial-well technic. Data from the first 33 cases of this series are presented in detail, to allow analysis by others of the basis for these conclusions.

THE accumulation of accurate information as regards operative mortality and results of surgery is basic to the advancement of the surgical management of any disease. It has been amply demonstrated by Lewis and Taufic,[1] Swan,[2] Gross and associates,[3] Bailey and associates,[4] Björk and Crafoord,[5] Gibbon,[6] Shumacker[7] and ourselves[8] that a number of technics of closure of atrial septal defects can be performed in man. It is likely that no one method in the near future will supplant all other technics at present in use. Advancement of knowledge in the treatment of this condition depends on the evaluation of the results obtained by each of these operative technics.

It is the purpose of this paper to present in detail the results of operation in our first 33 patients with atrial septal defect and left-to-right shunt. To Dec. 1, 1955, 59 patients with atrial septal defects and left-to-right shunts, either alone or in combination with right-to-left shunts, have been treated by the atrial-well technic (with two exceptions as noted later in this paper) at the Mayo Clinic. There have been three deaths in the entire series, including the one death (case 31) in the group reported here. The manner of death in this case during operation has been described in detail in a previous paper,[8] in which the patient was listed as case 11.

Although all of the patients to be discussed had atrial septal defects with left-to-right shunting of blood across the defect, many had additional complicating features. Some had a degree of right-to-left shunting, as well. The age, sex, and body surface area of the patients are listed in table 1, along with their status according to the New York Heart Association Classification. Only four patients were entirely asymptomatic. Results of closure are given in table 2. Only 21 patients had anatomically uncomplicated atrial septal defects, 12 patients having associated defects as indicated in table 3.

Material and Methods

Thirty-one of the 33 patients were operated on with the atrial-well technic of Gross and associates,[3] with minor changes in details of suturing. A suitable piece of noncompressed Ivalon sponge was used to close the defects. Modifications of this technic for patients with associated and more complicated defects were employed as described by us.[8] The cases here reported as cases 22, 24, 25, 23, and 26 are cases 1, 3, 4, 5 and 6 in the article detailing the methods employed in the surgical treatment of anomalous pulmonary venous connection.[9] In two of these a slight modification of the technic of Bailey and associates[4] was utilized.

Hemodynamic data concerned with the status of the circulation after closure of the defects are available in 31 of the 32 patients surviving operation, and are shown in table 3. In this, and in tables 1 and 4, the cases are grouped anatomically, and arranged in order of decreasing left-to-right shunt. In some patients the hemodynamic data were obtained at postoperative cardiac catheterization some weeks or months following operation. The technics of study employed at cardiac catheterization, including the routine use of dye-dilution curves recorded after injection of T-1824 into multiple

From the Mayo Clinic and Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

TABLE 1. *Patients Having Atrial Septal Defect*

Case	Age, years	Sex	Body surface, M.²		New York Heart Asso. Classification
			Pre-operative	Post-operative	
1	27	F	1.61	1.59	II
2	29	F	1.45	—	II
3	34	F	1.45	—	II
4	18	F	1.64	—	II
5	23	F	1.31	—	II
6	39	F	1.55	1.59	III
7	19	F	1.66	—	I
8	30	F	1.68	1.68	II
9	46	F	1.53	—	II
10	35	F	1.56	—	II
11	23	F	1.58	—	I
12	32	M	1.65	1.68	II
13	13	M	1.55	1.59	I
14	48	F	1.50	—	I
15	32	M	1.91	1.89	II
16	27	F	1.57	1.68	II
17	31	F	1.51	—	II
18	16	F	1.57	—	II
19	11	F	1.26	1.26	II
20	24	F	1.66	1.69	III
21	34	M	1.85	—	III
22	43	F	1.67	1.66	II
23	22	M	1.79	1.80	II
24	23	M	1.98	1.99	II
25	32	F	1.61	—	III
26	23	F	1.48	—	IV*
27	25	F	1.36	1.39	III
28	27	F	1.56	1.60	II
29	22	M	1.88	1.88	II
30	23	F	1.66	1.70	II
31	48	F	1.59	—	IV
32	4	M	0.64	—	IV
33	19	F	1.53	1.53	II

* Pregnant.

sites of the heart and great vessels, have been detailed by us elsewhere.[10-13] Calculations of the systemic and pulmonary flow were made in these patients by the method described by Swan, Burchell, and Wood, using oxygen saturation data.[14] Calculations of right-to-left shunts and estimations of left-to-right shunts from the dye-dilution curves were made by technics previously described from this laboratory.[15, 16] Estimation of the degree of preferential shunt from the right or left lung has been made on the basis of dye-dilution curves recorded after injection of the dye into the right and left pulmonary arteries.[17]

In other patients the hemodynamic data have been obtained at the time of operation, following closure of the defect. The technics of this procedure have been described elsewhere by us.[18] Briefly, through a catheter introduced through the atrial

TABLE 2. *Results of Closure of Atrial Septal Defects*

Condition	Excellent	Fair	Poor	Dead	Total
Atrial septal defect without associated defect	19*	2	0	0	21
Atrial septal defect with partial anomalous pulmonary venous connection	3	1	1	0	5
Persistent common atrioventricular canal	1	1	0	0	2
Atrial septal defect with complete anomalous pulmonary venous connection	1	0	0	0	1
Atrial septal defect with other associated defects	3	0	0	1	4
Total	27	4	1	1	33

* In one of these cases, evaluation is on clinical data alone. Thus in the total group, 32 have hemodynamic evaluation, of which 26 are considered an excellent result.

well, samples were withdrawn from the superior vena cava, the inferior vena cava and the right ventricle, and the oxygen saturations of these were determined by the use of the cuvette oximeter. At this time dye-dilution curves were recorded from the radial artery after the injection of dye through a venous catheter introduced previously through an antecubital vein and advanced so that the tip lay in the superior vena cava or an adjacent central vein.

In many of the cases studied postoperatively by cardiac catheterization, studies had been done in the operating room as well. Although in such cases the data collected in the operating room are not detailed, it can be stated that the agreement between the two sets of data is good.

Figure 1 is an example of the type of data that was collected.

RESULTS

Thirty-two of the 33 patients whose data are here presented are alive and well, one patient having died as noted previously. There is one case in which no postoperative physiologic studies are available (case 10). This patient was operated on relatively recently and was considered at operation to have a complete and secure closure. Since the technic has become standardized, in every instance in which it was believed that a complete and

ecure closure was obtained at operation, post-perative physiologic studies have verified it. t is, therefore, considered fair to classify this patient as an excellent result clinically, although hemodynamic evaluation cannot as yet be made.

The over-all results of operation in these cases are depicted in summary form in table 2. The hemodynamic data, obtained preoperatively and postoperatively, are presented in detail in tables 3 and 4. Table 3 includes the saturation data and dye-curve results, and table 4 presents the intracardiac, pulmonary artery, and systemic arterial pressures.

Some explanation of certain items of table 3 is required. The presentation is similar for the preoperative and the postoperative study. The oxygen saturation of blood withdrawn from the radial artery, superior vena cava, inferior vena cava, and the right atrium is indicated. The oxygen saturation of blood withdrawn from the pulmonary artery is given, unless no such sample was obtained, in which case the value for blood withdrawn from the right ventricle is given if available. All saturation data given were obtained while the patients were breathing air. Values for systemic and pulmonary flow are given, calculated from oxygen uptake and saturation data when these are available.[14]

The magnitude of the left-to-right shunt as estimated by the dye-dilution pattern after central injection of T-1824 is indicated by grade, grade 0 being no detectable left-to-right shunt, and grade 5 being complete anomalous venous drainage from a lung. Figure 2 indicates the correlation between the degree of shunting and the pattern of the curve for each grade. These curves are illustrative of the contour recorded after injection of dye into a right or left pulmonary artery. The contour of the indicator-dilution curves recorded after injection into the right and left pulmonary arteries indicates the degree of left-to-right shunting of the blood from each lung, and these separate values are included in table 3. It is noted that in ordinary atrial septal defect the right lung may have a more abnormal dye-curve pattern than the left lung; there is, in other words, preferential shunting from the right lung. In the patients with anomalous pulmonary venous connection of the right lung and with atrial septal defect, the preferential shunting from this lung is either severe or complete, the latter instance producing the grade-5 curve. It is to be noted also that curves of a pattern compatible with grade 1 to 3 shunting are obtained from injection of dye into the main pulmonary trunk in atrial septal defect, as demonstrated in table 3. Grade 2- and 3-curves are indicative of a 50 to 80 per cent left-to-right shunt.

A patient is considered to have an excellent result from operation when no residual shunt is found. This outcome was present in 20 of the 26 cases termed excellent. Of the remaining six cases, three had a suggestion of a very small left-to-right shunt from saturation data or dye curves, but the complete study could not with certainty establish its presence. These cases are quite possibly hemodynamically normal. In three others the results are considered excellent, in spite of a small residual shunt, because the shunts appear too small to be of functional significance. Four patients are considered to have only fair results, although all are symptomatically improved, for three have residual left-to-right shunts of 35 to 40 per cent, and one (case 26) had a residual right-to-left shunt of 20 per cent when studied 2 weeks postoperatively. She was not visibly cyanosed. Pregnant at the time of operation, she subsequently had a normal delivery and now considers herself normal. Preoperatively, she had significant disability. The data are self-evident in the one poor result, the first case in which operation was performed by us, as discussed later in this paper.

Atrial Septal Defect Without Associated Defect. There are 21 patients with large atrial septal defects without associated lesions who have been operated on. No deaths occurred in this group. There are no poor results in this group and 18 are considered hemodynamically to have an excellent result. In 1 patient no postoperative data are available, as mentioned previously.

Atrial Septal Defect With Partial Anomalous Pulmonary Venous Connection. There are five patients with atrial septal defects and partial anomalous pulmonary venous connection. The

TABLE 3. *Data from Cardiac Catheterization*

Case	Preoperative cardiac catheterization														Date of operation	Postoperative cardiac catheterization											Hemodynamic results of surgery
	Date	O_2 saturation (%) of blood					Flow, L./min./M.²		Shunts† in % of flow		Magnitude of L-R shunt from dye curve‡			O_2 capacity, volume %		Interval between operation and post-operative study	O_2 saturation (%) of blood					Flow, L./min./M.²		Shunts in % of flow		Magnitude of L-R shunt from dye curve	
		Radial artery	SVC	IVC	RA	RV* or PA	Pulmonary	Systemic	L-R	R-L‡	Main pulmonary artery	Right lung	Left lung				Radial artery	SVC	IVC	RA	RV* or PA	Pulmonary	Systemic	L-R	R-L‡		
Atrial septal defects without associated defect																											
1	6/23/53	98	70	84	95	93	13.8	3.0	80	—§	2-3	3	2	16.7	8/11/53	7 months	98	70	85	87	89	6.3	4.2	35	10	2	Fair
2	11/28/51	96	66	88	95	92	20.7	5.6	75	—	2-3	—	—	16.3	4/23/54	3 weeks	96	69	—	82	—	—	—	40‖	—§	1	Fair
3	5/24/54	97	68	79	92	93	10.2	2.8	75	—	2	3	1	17.0	6/9/54	at operation	98	77	81	—	83*	—	—	15	—	0	Excellent
4	elsewhere	98	90	92	—	98	—	—	75	—	2	—	—	—	12/21/54	at operation	97	94	90	—	90*	—	—	0	0	0	Excellent
5	1/24/55	97	72	83	93	93	11.3	2.6	75	5	3	3-4	2	15.3	2/19/55	at operation	98	78	75	—	76*	—	—	0	0	0	Excellent
6	2/25/54	99	75	83	89	93	11.5	3.3	70	0	2	3	1	17.8	3/10/54	14 months	97	67	72	75	73	3.0	2.7	10	0	0	Excellent
7	7/15/54	98	74	79	87	92	10.6	3.1	70	—	2-3	4	—	18.3	7/17/54	at operation	98	79	91	—	82*	—	—	0	—	0	Excellent
8	1/11/54	97	81	88	94	95	13.3	4.2	70	5	2-3	3	1	16.4	2/5/54	11 months	98	75	84	82	82	3.6	3.6	0	0	0	Excellent
9	1/6/55	94	67	—	90	90	8.8	2.6	70	—	2	2-3	—	18.8	1/11/55	at operation	96	82	87	—	75*	—	—	0	0	0	Excellent
10	6/3/54	98	62	78	82	89	7.6	2.6	65	0	2	2	—	18.1	11/26/54	—	—	—	—	—	—	—	—	—	—	—	No studies
11	9/16/54	98	71	82	90	91	10.9	3.9	65	0	2-3	2	2	17.4	9/23/54	at operation	97	81	92	—	87	—	—	0	—	0	Excellent
12	3/17/54	99	75	86	91	93	7.4	3.0	60	5	2	2	—	19.6	8/18/54	4 months	—	—	—	—	—	—	—	—	—	0-1	Excellent
13	5/28/54	97	76	80	87	91	13.1	5.2	60	0	2	—	3	19.4	6/4/54	4 months	99	79	80	80	77	3.5	3.5	0	0	0	Excellent
14	1/25/55	96	65	70	86	85	5.8	2.2	60	<5	2	2	—	17.1	2/1/55	at operation	96	73	56	—	62*	—	—	0	0	0	Excellent
15	1/17/55	98	63	75	88	89	6.3	2.5	60	0	2	3-4	2	16.8	2/15/55	3 months	98	75	—	75	73*	3.2	3.2	0	—	0	Excellent
16	5/10/54	92	73	83	89	92	10.3	4.4	55	15	2	4	1	19.1	5/19/54	1 year	99	78	84	84	81	3.5	3.5	0	0	0	Excellent
17	1/20/55	98	74	83	87	89	11.5	5.2	55	5	2	3	1	18.8	2/22/55	at operation	97	68	54	—	58	—	—	0	0	0	Excellent
18	4/15/54	99	76	78	87	90	7.2	3.5	50	—	1-2	—	—	18.0	6/5/54	at operation	97	91	92	—	89*	—	—	0	—	0	Excellent
19	6/15/53	96	83	83	90	90	9.6	5.0	50	5	1-2	2-3	—	17.6	6/2/54	3 months	98	66	76	65	—	—	—	0	—	0	Excellent
20	10/6/54	93	67	77	88	87	6.4	3.5	45	20	2	3	—	19.9	10/16/54	10 months	97	70	—	76	75	3.5	3.5	0	0	0	Excellent
21	1/27/55	96	59	71	83	80	3.4	2.2	35	—	2	2	—	20.1	2/17/55	at operation	98	68	68	—	71*	—	—	10	0	0	Excellent
Atrial septal defect with partial anomalous pulmonary venous connection																											
22	2/9/53	96	66	77	95	94	11.5	2.4	80	—	3	5	1	18.3	2/12/53	13 months	98	67	—	92	89	6.4	2.1	65	0	2	Poor
23	6/3/53	98	77	84	92	95	14.2	3.1	80	—	2-3	4	1	22.4	8/18/53	5 months	97	71	82	81	77	3.6	3.6	0	—	0	Excellent
24	2/5/54	95	63	73	85	87	8.4	2.8	60	0	2	5	1	21.2	3/25/54	5 months	97	77	79	79	78*	3.6	3.6	0	—	0	Excellent
25	7/8/54	97	70	90	94	92	8.4	4.5	45	0	2	5	1	19.2	7/29/54	at operation	—	—	—	—	—	—	—	—	—	0	Excellent
26	1/10/55	94	64	76	86	84	4.8	3.5	30	25	2	2	—	16.8	1/25/55	2 weeks	91	58	—	66	64*	4.8	6.1	0	20	0-1	Fair

Persistent common atrioventricular canal																									
27	11/16/54	97	73	84	89	94	14.7	3.3	75	0	2–3	3	2	17.7	1/6/55	7 months	97	75	85	86	88	6.4	4.2	35	0	1–2	Fair
28	11/25/53	98	62	78	88	91	9.4	2.9	70	5	2	3	2	17.4	1/5/54	3 months	97	67	72	73	75	3.1	3.1	0	0	0	Excellent
Atrial septal defect with complete anomalous pulmonary venous connection																									
29	6/2/54	92	64	75	91	92*	—	—	80	20	3	—	—	15.7	6/11/54	3 weeks	90	66	68	68	65	3.8	3.8	0	0	0–1	Excellent
Atrial septal defect with other¶ associated defects																									
30	9/28/53	92	50	69	84	88	5.6	1.7	70	20	3	—	3	18.7	10/16/53	1 year	99	70	77	76	77*	3.8	3.4	10	0	0–1	Excellent
31	3/31/54	97	60	74	87	87	8.1	2.5	70	—	2	3–4	1	20.5	4/5/54	Died	—	—	—	—	—	—	—	—	—	—	Death
32	9/15/54	97	79	85	96	92	10.2	5.8	65	0	2	4	—	15.2	9/21/54	3 months	98	—	—	—	—	—	—	—	—	0	Excellent
33	1/20/54	97	60	75	74	71	4.1	4.1	±	15	1–2	—	1	15.0	1/25/54	9 months	95	58	78	67	68	2.8	2.8	0	0	0	Excellent

* Denotes RV sample instead of PA sample. SVC: Superior vena cava; IVC: Inferior vena cava; RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery.

† L-R shunt is percentage of total pulmonary flow consisting of shunted blood. R-L shunt is percentage of total systemic flow consisting of shunted blood.

‡ R-L shunts calculated on the basis of dye curves recorded following dye injection into the superior and inferior venae cavae (15).

Graded on a basis of 1 to 5.

§ — Denotes those cases in which a dye injection into the inferior vena cava was not done, and superior vena cava curves showed no R-L shunt.

‖ L-R shunt was calculated using inferior vena cava saturation as 6% higher than superior vena cava, and assuming that the oxygen saturation of right atrial and pulmonary artery blood was equal.

¶ In case 30, mitral stenosis; in case 31, mitral insufficiency; in case 32, coarctation of the aorta; in case 33, pulmonary stenosis.

TABLE 4. *Data from Cardiac Catheterization*

Case	Preoperative cardiac catheterization						Postoperative cardiac catheterization						
	Pressures in mm. Hg					TPR, dynes sec. cm.$^{-5}$	Interval between operation and postoperative study	Pressures in mm. Hg				TPR, dynes sec. cm.$^{-5}$	
	Radial artery	RA	RV	PA	PA wedge			Radial artery	RA	RV	PA	PA wedge	
1	117/62	15/6	44/13	35/20	—	150	7 months	108/64	12/5	35/7	33/29	18/4	264
2	114/69	12/6	40/6	35/16	15/0	90	3 weeks	102/46	5/0	32/4	—	—	—
3	102/60	4/0	34/9	32/10	10/6	75	at operation	102/58	9/5	50/8	—	—	—
4	143/88*	16/13*	54/5*	—	—	—	at operation	102/62	10/6	33/7	—	12/7†	—
5	104/66	9/3	62/4	44/20	12/9	107	at operation	121/73	4/0	40/0	—	9/5†	—
6	100/45	6/3	31/0	28/8	8/5	70	14 months	140/70	2/–2	18/3	15/6	—	150
7	116/58	10/5	25/4	21/9	12/6	60	at operation	106/54	9/7	37/12	—	—	—
8	114/62	7/3	25/2	23/8	11/8	150	11 months	118/57	5/2	22/7	20/10	—	130
9	114/64	4/0	21/6	22/10	—	84	at operation	121/71	6/4	24/3	—	11/5†	—
10	124/67	8/4	25/5	23/10	8/6	95	—	—	—	—	—	—	—
11	125/79	8/3	38/5	34/12	15/8	80	at operation	132/70	3/–1	25/0	—	—	—
12	95/56	8/2	30/8	23/9	13/9	90	4 months	—	—	—	—	—	—
13	90/60	5/1	40/6	37/11	14/6	60	4 months	104/57	6/0	24/0	23/12	11/6	140
14	117/65	4/0	26/4	26/12	—	156	at operation	112/86	12/7	29/9	—	14/11†	—
15	110/60	11/5	60/12	66/22	18/10	244	3 months	109/53	5/2	48/6	—	—	—
16	135/75	6/1	37/2	30/15	—	100	1 year	126/68	4/0	32/5	15/5	7/5	110
17	135/76	7/1	—	27/11	—	74	at operation	80/60	4/2	29/1	—	—	—
18	123/78	5/1	37/5	28/10	—	120	at operation	128/65	7/4	—	—	11/5†	—
19	102/63	2/0	27/4	14/8	—	60	3 months	108/62	5/2	23/1	21/9	11/6	210
20	104/59	5/2	70/7	69/37	9	375	10 months	115/64	13/4	34/5	41/22	12/10	370
21	120/72	8/4	60/5	65/22	8/5	540	at operation	120/72	9/7	72/7–16	—	11/6†	—
22	107/61	9/3	48/8	37/19	—	105	13 months	90/41	5/2	35/2	32/14	16/6	150
23	129/72	7/1	41/8‡	28/12‡	11/4	55	5 months	123/70	8/1	32/14‡	23/14‡	10/7	210
24	105/70	10/6	28/5	27/14	12/7	105	5 months	101/57	4/1	20/5	—	—	—
25	106/12	3/1	34/1‡	27/10‡	—	95	at operation	115/77	10/6	32/11	—	15/14	—
26	106/53	7/1	81/0	86/33	8/0†	58	2 weeks	117/58	6/2	54/4	—	8/2†	—
27	114/57	7/2	29/4	25/10	11/5	58	7 months	118/55	8/1	23/7	19/10	12/7	160
28	106/71	12/6	26/4	23/8	—	75	3 months	115/60	3/–1	18/0	15/3	—	110
29	—	9/4	34/6	—	—	—	3 weeks	112/63	14/4	24/1	—	—	—
30	72/57	22/11	34/15	34/16	26/16	190	1 year	106/64	2/1	22/3	—	—	—
31	101/74	22/14	127/43	127/9	—	390	—	—	—	—	—	—	—
32	123/58	8/5	53/6	50/8	8/6	395	at operation	90/45	30/25	45/10	—	—	—
33	129/67	7/3	108/7	12/7	12/6	130	9 months	114/63	7/2	32/–1	14/8	9/5	205

* Study done with patient under anesthesia just prior to operation; catheterized previously elsewhere.

† Values are left atrial or pulmonary vein pressures.

‡ With the exception of these 3 instances pulmonary artery and right ventricular pressures were measured on the continuous pressure recording obtained when the catheter tip was withdrawn from the pulmonary artery to right ventricle.

RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery; TPR: Total pulmonary resistance.

technic of repair of these anomalous pulmonary venous connections in association with the repair of the atrial septal defects has been presented in detail elsewhere.[9] Case 22 was the first case of repair of an atrial septal defect in our group. It was known at operation that a significant although relatively small residual defect remained. There continues to be a large (65 per cent) left-to-right shunt through this defect. This case is the one adjudged a poor result. In case 26, mentioned in an earlier paragraph, in which the patient had a bidirectional shunt and severe pulmonary hypertension, in whom the atrial well could not be employed because of the anatomy of the combination of defects, there is no postoperative left-to-right shunt but there is a residual right-to-left shunt from the region of the superior vena cava. This case is considered to be a fair result. These studies were in the

immediate postoperative period on this case, and there may be some betterment of the situation as time elapses. The remaining 3 cases in this group have complete repairs hemodynamically and results are termed excellent.

Persistent Common Atrioventricular Canal. There are two cases of persistent common atrioventricular canal. One case, studied three months postoperatively, is hemodynamically normal and the result is considered excellent. The second case was studied seven months postoperatively. There was a 35 per cent left-to-right shunt, mainly at the ventricular level. The preoperative left-to-right shunt was calculated to be 75 per cent. This is hemodynamically only a fair result.

Atrial Septal Defect With Complete Anomalous Pulmonary Venous Connection. One case of atrial septal defect with complete anomalous

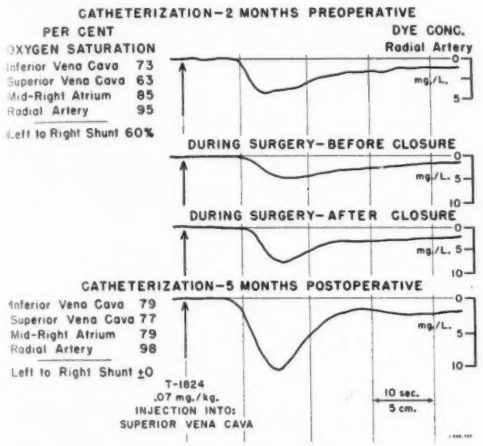

FIG. 1. Demonstration of complete closure of an atrial septal defect during and five months after operation in a 23 year old man (case 24). The upper panel of the figure shows the data recorded during cardiac catheterization two months before operation. On the left are the blood oxygen saturation values obtained by drawing blood samples from the right atrium and venae cavae through a cuvette oximeter, the samples being in rapid succession. There is demonstrated a marked increase in oxygen saturation of blood in the right atrium as compared to that in the venae cavae, and the left-to-right shunt is calculated from the saturation data to be 60 per cent of the total pulmonary flow. An arterial-dilution curve, shown on the right, recorded at the radial artery after injection of T-1824 into the superior vena cava shows marked prolongation of the disappearance slope, indicating the presence of a large arteriovenous shunt. The two dye curves (middle panels) recorded during surgery are shallow, in part owing to the lesser sensitivity of the recording system. The curve recorded prior to closure of the defect, however, is similar to the preoperative curve, whereas the curve after closure of the defect with an Ivalon sponge depicts a normal contour. The lower panel, showing data from the postoperative cardiac catheterization, gives no evidence of the previous increased oxygen saturation of the blood in the right atrium, and the contour of the dye-dilution curve is normal.

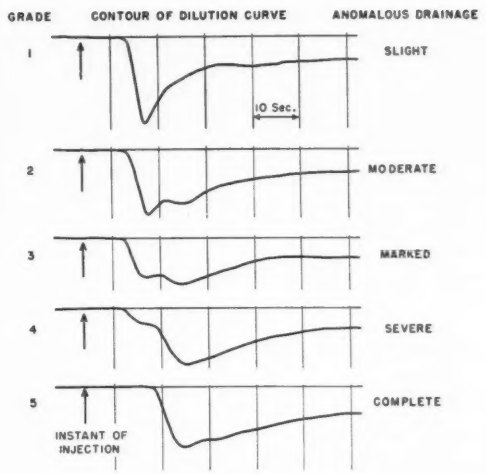

FIG. 2. Diagrammatic representation of indicator-dilution curves indicating left-to-right shunts of increasing magnitude. The curves indicate the contour obtained in a dye-dilution curve recorded after the injection of dye into a right or left pulmonary artery leading to a lung with various degrees of anomalous venous drainage. The numbers on the left represent the magnitude of shunt in grade 1 to 5. The first curve is indicative of a slight anomalous drainage, 20 to 30 per cent left-to-right shunt, whereas the contour of the curve indicating a grade 3 shunt is consistent with a 70 to 80 per cent left-to-right shunt. The pattern seen in curve 4 is one of severe anomalous drainage, and the contour of curve 5 is seen only with complete anomalous drainage from the involved lung. The contour seen in the first three grades depicted can also be obtained from injection into the main pulmonary artery in patients with atrial septal defect and left-to-right shunt, with or without various degrees of anomalous pulmonary venous connection. The distinction between anomalous pulmonary venous connection and drainage has been made previously by us.[19]

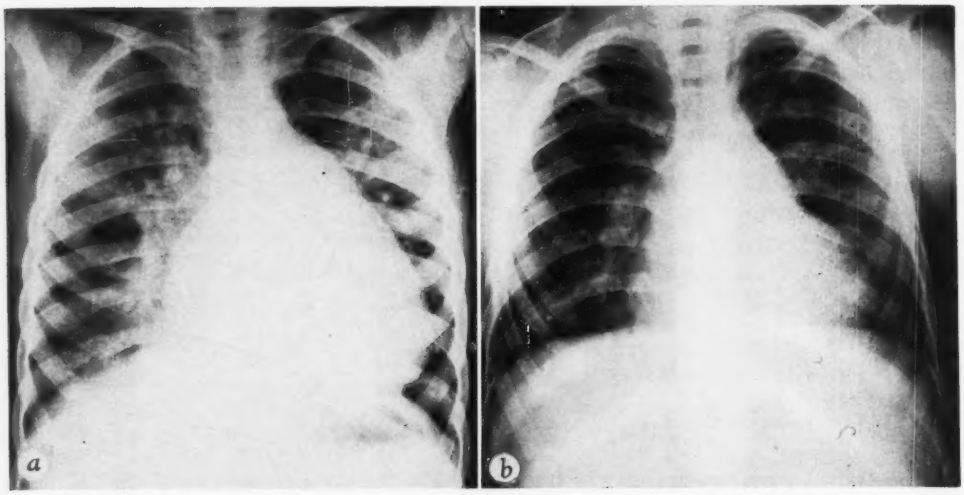

FIG. 3. Preoperative and postoperative roentgenograms of the chest of a 5 year old boy who had repair of an atrial septal defect followed in 3 months by repair of a concomitant coarctation of the aorta. The first roentgenogram was taken two weeks before the atrial septal defect was repaired. The second roentgenogram was taken 6 months after the correction of the coarctation. The two films were taken about nine and a half months apart.

pulmonary venous connection to the right atrium was repaired by the use of an Ivalon sponge to channel the pulmonary venous return across the atrial septal defect into the left atrium. There is a suggestion of a minimal persistent left-to-right shunt 3 weeks postoperatively in the dye-dilution curve, but the saturation data do not indicate this. The patient is probably hemodynamically normal.*

Atrial Septal Defect With Other Associated Defects. There is one patient with mitral stenosis and an atrial septal defect in whom a combined repair was carried out. She is adjudged to have an excellent result in spite of the presence of a very small residual left-to-right shunt. One patient with severe pulmonary hypertension and mitral insufficiency associated with atrial septal defect died during operation, as noted in a previous paragraph. One patient, a 5-year-old boy in severe cardiac failure, had a coarctation of the aorta and an atrial septal defect. The atrial septal defect was repaired, and 3 months later the coarctation was repaired. Indicator-dilution curves done at the time of the coarctation repair were entirely normal, indicating complete closure of the atrial septal defect. The patient is now clinically asymptomatic. Figure 3 compares the chest films taken of this patient 2 weeks before closure of the atrial septal defect and 6 months after correction of his coarctation.

* This patient has now been recatheterized one and one-half years postoperatively. There are no shunts, and he is hemodynamically normal. The data from the last study are not in table 3.

COMMENT

The experience herein presented with a series of atrial septal defects, 21 of them being large defects without associated anomalies, and 12 of them being complicated in one form or another, indicates that an excellent result at a low operative risk can be obtained in this disease. With an operative mortality of 1 case in 33, with an excellent result in 27 of the 32 surviving patients, and a fair result in 4 of the remaining, it seems now justified to advise repair of atrial septal defects in all patients with significant physiologic derangement resulting from this anatomic malformation. Further, in the subsequent 26 cases, bringing the entire series to 59 cases, closures have all been judged to be complete.

Some discussion of changes in pulmonary

rtery pressure should be made, although the lata in this regard are not striking. Table 4 llustrates the fact that after closure of the trial septal defects there is in nearly all nstances a mild drop in pulmonary artery ressure even when it has been within the range f normal prior to operation. Table 4 also llustrates the good results from pulmonary alvotomy in association with the repair of an trial septal defect in case 33.

Summary

1. The technics of physiologic study of atrial septal defects preoperatively, in the operating room, and postoperatively have been outlined.

2. In our first 33 consecutive cases with left-to-right shunts, the results of operative closure of atrial septal defects were excellent in 27 cases, fair in 4 cases, and poor in 1 case. In one case, there was a postoperative death. This series of cases now includes 59 cases.

3. It is concluded that operation for atrial septal defect may be done at a low risk with an excellent prospect of a good result.

Summario in Interlingua

Experientias con le tractamento chirurgic de 59 casos de defecto atrio-septal representa un testimonio al securitate e efficacia del procedimento utilisante le technica del puteo atrial. Es presentate datos detaliate relative al 33 prime casos de iste serie con le objectivo de permitter a alteros le analyse del base de nostre conclusiones.

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The Use of Aramine in Clinical Shock

By George H. Stechel, M.D., Stanley I. Fishman, M.D., George Schwartz, M.D., Hyman Turkowitz, M.D., Peter F. Madonia, M.D., and Arthur Fankhauser, M.D.

The use of vasopressor agents in shock is of established value and has become a common form of treatment. Aramine was used in over 250 unselected cases of shock of varied etiology, of which 42 cases are reported in some detail. This agent continues to produce a vasopressor effect after the actual cessation of administration, and its use is characterized by ease in maintaining the desired blood pressure level. Distressing side effects, such as thrombophlebitis or tissue slough, do not occur.

THE use of Aramine, a sympathomimetic amine, in normal subjects was reported in 1954.[1] This study indicated the effectiveness of this drug as a vasopressor and suggested certain advantages over other commonly used vasopressors. Therefore, an extended study of the effects of Aramine in clinical shock states was undertaken, and the results are herewith reported.

Method

Every case admitted to the First Division Medical Service, Kings County Hospital Center, in which the use of a vasopressor was indicated received Aramine.* In each case the drug was administered intravenously diluted in 1000 ml. of 5 per cent dextrose in water. Early in the study, 50 mg. of Aramine was diluted in 1000 ml. of 5 per cent dextrose in water. The infusion was initiated at a rate of 80 to 100 drops per minute, and then regulated according to the blood pressure response. If the response was inadequate after 10 minutes, another 25 mg. of Aramine was added to the infusion. By this method, it was soon found that a higher concentration of Aramine was both safe and preferable. Three hundred milligrams of Aramine per 1000 ml. of dextrose in water soon became the concentration of choice. The blood pressure was recorded every minute, for the first 5 to 10 minutes, then every 5 minutes until the blood pressure was maintained at the desired level, and finally recordings were made as indicated by the severity of the case and duration of treatment. In those cases in which the blood pressure did not respond quickly, norepinephrine was substituted.

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* Aramine was supplied by Sharp and Dohme, West Point, Pa.

Results

Aramine has now been used in approximately 250 cases of clinical shock. Of these, 42 cases are reported in some detail. In each case, the diagnosis has been verified beyond reasonable question. These results are tabulated (table 1). The remaining 208 cases are not included in this report because there was insufficient data concerning the diagnosis or the response to the drug.

Of these 42 cases, 15 (36 per cent) left the hospital alive, 27 (64 per cent) died. The study necessarily included a high percentage of "poor-risk" cases, as noted in table 1. The patients' ages ranged from 28 to 87 years, with an average of 63 years.

The blood pressure did not respond in 6 cases (14 per cent). Norepinephrine was substituted in 12 patients in whom no prompt response with Aramine was obtained, all of whom died, despite this measure. There was no blood pressure response to norepinephrine in 11 of these 12 patients. The twelfth patient showed an adequate blood pressure response, but subsequently died.

All patients were in marked clinical shock, with initial blood pressures varying from 0/0 to 110/70 (the latter, previously a hypertensive patient). Sixteen of these patients were in shock as a result of proved myocardial infarction. Six (38 per cent) of these 16 patients survived.

Comment

As noted in table 1, a wide variety of clinical entities are represented. In addition, a considerable number of surgical shock states were

TABLE 1.—*Results in 42 Cases of Shock*

Patient	Age	Sex	Diagnosis	Result	Initial Blood Pressure	Blood Pressure Response	Duration of Therapy
1	62	M	Congestive heart failure, pneumonia	Alive	70/40	120/80	16 hours
2	71	M	Myocardial infarction	Died	0/0	120/80	8 hours
3	65	F	Gastrointestinal bleeding	Alive	0/0	100/60	1.5 hours
4	55	F	Gastrointestinal bleeding	Alive	70/30	150/50	16 hours
5	48	M	Gastrointestinal bleeding	Alive	60/40	115/80	2 hours
6	34	M	Hepatic coma	Died	46/30	110/60	5.75 hours
7	28	M	Ventricular tachycardia	Alive*	0/0	0/0	25 minutes
8	52	F	Acute yellow atrophy	Died	60/40	60/40	15 minutes
9	64	M	Myocardial infarction	Died	0/0	0/0	55 minutes
10	87	F	Granulocytic leukemia, myocardial infarction	Died	80/42	0/0	55 minutes
11	58	F	Myocardial infarction, diabetic coma	Alive	88/60	110/80	43.5 hours
12	50	M	Acute bacterial endocarditis	Alive†	50/30	150/100	120 hours
13	68	M	Myocardial infarction, ventricular fibrillation	Died	90/60	0/0	1 hour
14	79	F	Myocardial infarction	Alive	40/0	110/70	17.5 hours
15	58	M	Dissecting aneurysm	Died	40/0	130/100	9.5 hours
16	85	M	Bronchogenic carcinoma	Died	80/40	120/86	10 hours
17	53	F	Aplastic anemia with hemorrhage	Died	45/0	120/65	4 hours
18	55	M	Pulmonary infarction, cor pulmonale, pneumonia, and empyema	Died	56/34	110/46	2.5 hours
19	55	M	Cor pulmonale	Alive	76/60	110/85	43 hours
20	39	M	Acute hemorrhagic pancreatitis, acute yellow atrophy	Died	0/0	120/70	55 hours
21	45	M	Myocardial infarction	Died	40/20	130/90	50 hours
22	63	M	Myocardial infarction	Died	0/0	0/0	1 hour
23	65	M	Perforated duodenal ulcer	Died	68/40	120/70	14 hours
24	63	M	Carcinomatosis with hematemesis	Died	54/0	100/60	18 hours
25	60	F	Myocardial infarction	Died	78/50	100/70	20 hours
26	80	F	Myocardial infarction	Alive	30/0	110/70	1 hour
27	74	F	Myocardial infarction	Alive	60/40	150/80	5 hours
28	72	M	Cerebral vascular accident	Died	70/50	120/70	1.5 hours
29	82	F	Myocardial infarction	Died	80/60	120/80	2 hours
30	62	M	Myocardial infarction, ventricular tachycardia	Alive	0/0	140/110	1 hour
31	60	M	Bronchogenic carcinoma	Died	80/38	130/50	10 hours
32	37	M	Heat prostration	Died	0/0	90/60	30 minutes
33	65	M	Hypertensive cardiovascular disease, pulmonary hemorrhage	Alive	110/70	150/90	30 minutes
34	65	F	Myocardial infarction	Died	0/0	0/0	30 minutes
35	44	F	Uremia with gastrointestinal bleeding	Died	70/50	150/90	24 days
36	51	F	Atrial fibrillation, multiple embolizations	Died	80/40	150/90	16 days
37	28	M	Paraldehyde intoxication	Alive	80/60	140/90	16 hours
38	78	M	Myocardial infarction	Died	0/0	120/90	1.5 hours
39	60	M	Myocardial infarction	Died	80/0	120/70	13.5 hours
40	57	M	Rheumatic heart disease, ventricular tachycardia	Died	0/0	0/0	5 minutes
41	60	M	Subacute bacterial endocarditis, multiple embolizations	Died	80/40	130/70	5 days
42	49	M	Gastrointestinal bleeding	Alive	80/40	140/80	3 days

* Blood pressure rose coincident with return of regular sinus rhythm.

† Died 20 days after cessation of Aramine therapy.

eated with Aramine on the surgical services, ith results comparable to those reported here. I should be noted that it was not the purpose this study to determine the efficacy of a vasopressor in the various clinical entities, but merely to determine the efficacy of Aramine as a vasopressor. No conclusion is intended, nor should be drawn, as to the advisability of sub-

stituting a vasopressor for blood or fluid replacement, for example. In cases of hemorrhage in this study, Aramine in infusions was used only until matched blood was available.

Particular mention is given the use of Aramine in shock due to myocardial infarction, solely because of the current interest in the use of vasopressors in this condition. No blanket endorsement for the use of Aramine, or any other vasopressor, in shock due to myocardial infarction is intended.

With 300 mg. per 1000 ml. of 5 per cent dextrose in water, a rise in blood pressure to adequate levels can be anticipated within 5 minutes. Lack of response within 10 minutes usually indicated complete failure of vasopressor therapy. In many instances, therapy with Aramine was maintained for long periods of time (24 days in one case). In all cases it was noted that after discontinuing Aramine, the blood pressure gradually fell to levels that caused some alarm to the resident staff and it seemed advisable to restart Aramine immediately. In most instances, however, it was found that reinstitution of therapy was unnecessary, for the patients' blood pressures gradually readjusted to withdrawal of the pressor agent over a period of hours.

Advantages of Aramine over other pressor agents compared in the pilot study[1] were verified in the present study and several new advantages were noted. Relative ease of control of blood pressure levels was again noted; the blood pressure rose rapidly to the desired level, without the meteoric rise to excessive levels so often encountered with other agents. When Aramine was stopped, intentionally or otherwise, the fall in pressure was a gradual one over a period of 10 to 15 minutes, as contrasted with the precipitous drop in pressure often seen on withdrawal of other pressor amines. This characteristic is of particular advantage in cases where extended therapy is necessary and eventual dislodging of the needle from the vein is a practical certainty. The continued pressor effect allows adequate time for reinserting the needle in a new vein.

In no instance was there any deleterious result from infiltration of the tissues by infusion fluid containing Aramine. In fact, unintentional intramuscular administration of undiluted Aramine in two instances caused no untoward effects. In using another potent pressor agent at this hospital, threading a polyethylene tube through the infusion needle into the vein for several inches has become common practice in an attempt to prevent thrombophlebitis or distressing tissue sloughs. No such precaution is necessary in using Aramine; neither slough nor thrombophlebitis was noted in any of the cases studied.

Summary

Experiences with the use of Aramine in clinical shock of varied etiology in over 250 cases is described. Aramine possesses advantages that make it a safe and useful agent in conditions where a potent vasopressor drug is indicated.

Summario in Interlingua

Es describite experientias con Aramina in plus que 250 casos de choc clinic de varie etiologias. Aramina possede avantages que rende lo un utile e secur agente in conditiones in que le uso de un potente droga vasopressori es indicate.

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The Electrocardiographic Effects of Hypocalcemia Induced in Normal Subjects with Edathamil Disodium

By JACK T. BECHTEL, M.D., JEFFERSON E. WHITE, M.D. AND E. HARVEY ESTES, JR., M.D.

In the past, it has not been possible to study the electrocardiographic effects of hypocalcemia in normal subjects. Edathamil disodium is a powerful chelating agent with a strong affinity for ionic calcium when given intravenously. This agent was used to produce hypocalcemia in normal subjects so that electrocardiographic effects could be studied. The major changes produced in the electrocardiogram with the induction of hypocalcemia were shortening of the R-R interval, prolongation of the RS-T and Q-T intervals, all of which were proportional to the degree of hypocalcemia. No change in the spatial P, QRS and T vectors, no T wave flattening or inversion and no elevation or depression of the RS-T segment appeared with hypocalcemia.

IN THE past, it has been necessary to study the effects of hypocalcemia in the presence of disease. Since many factors in ill patients tend to influence the electrocardiogram, it has been difficult to be certain which changes in such patients were due only to hypocalcemia. The disadvantages of such electrocardiographic studies are obvious.

Since edathamil disodium is a complexing agent which has a strong affinity for calcium and will reduce serum ionized calcium when injected intravenously, it was felt that this agent would prove useful in defining electrocardiographic changes secondary to relatively uncomplicated hypocalcemia in normal persons.

Carter and Andrus[1] first reported Q-T prolongation in hypocalcemia tetany in 1922. Since then numerous studies of the electrocardiographic changes occurring with hypocalcemia in various disease states have been reported.[2-10] Many early investigators utilized only one or two electrocardiographic leads in reporting RS-T segment, Q-T interval and T-wave changes. Often other serum electrolytes were present in abnormal concentrations or were not determined, and these studies have led to many conflicting reports. In more recent years, however, several investigators have attempted to clarify this subject by utilizing more leads,[9-11] correcting values of the Q-T intervals for rate,[4, 9-11] and using better methods for the measurement of intervals.[11-13] The present authors are aware of no prior studies concerning the electrolyte and electrocardiographic changes during hypocalcemia in otherwise normal subjects.

METHOD

Seven subjects, all of whom were considered to be free of organic disease, were selected for study. In five of these subjects an intravenous infusion of edathamil disodium (3 Gm. in 400 ml. of solution at a pH of 7.4 to 7.8) was begun at zero time. In the remaining two subjects an intravenous infusion of edathamil calcium-disodium (3 Gm. in 400 ml. of solution at a pH of 7.4) was begun.* The infusion

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* Each gram of edathamil disodium (Na_2 EDTA) can chelate 108 mg. of calcium at a pH of 7.4, and in this combination the calcium is not ionized. At this pH edathamil disodium is actually a mixture of the disodium and trisodium salts, but for convenience will be termed edathamil disodium (Na_2 EDTA).

Edathamil calcium-disodium (Ca Na_2 EDTA) combines with no additional calcium. This makes it a useful preparation to use as a control to insure that the changes seen were due to hypocalcemia and not to the ethylene-diaminetetraacetate portion of the molecule or to the associated sodium and potassium changes which are similar after the injection of either substance.

was completed at an average time of 20.4 minutes (15 to 27 minutes). The vehicle (400 ml. of solution) was 5 per cent glucose in subjects 1 and 2; all others received normal saline. Blood samples for plasma sodium, potassium, calcium, and phosphate determinations were withdrawn at frequent intervals for the first two hours, then hourly for four to six hours. Electrocardiograms were recorded before the infusion and at the time blood specimens were withdrawn.

Electrocardiograms were recorded with a Sanborn direct-writing electrocardiograph at standard speed (25 mm. per second) and a Sanborn twin-beam photographic electrocardiograph at triple standard speed (75 mm. per second). The 12 standard leads were taken with the direct-writing instrument and selected leads for study were obtained with the twin-beam photographic instrument.

Electrocardiographic Measurements. In the limb leads, measurements were carried out in that lead in which QRS and T complexes were of greatest magnitude. In all cases studied this was lead II. In the precordial leads, measurements were carried out in the first lead lateral to the zone of QRS transition which showed large R waves, usually V_3 or V_4. Standardization for amplitude was checked in each lead, and suitable correction was made when necessary. The various intervals were measured by the technic of Lepeschkin and Surawicz[11, 12] with the following modifications: (1) both the initiation and termination of the T wave were measured by the tangential method and (2) the points at which tangents drawn to the ascending and descending limbs of the T wave intersected a line drawn parallel to the baseline through the S-T junction were considered as the beginning and end of the T wave. The intervals measured were as follows: (1) beginning of QRS to the end of T (Q-T), (2) beginning of QRS to the beginning of T (Q-oT), (3) beginning of QRS to apex of T (Q-aT), (4) beginning of T to the end of T (T), (e) beginning of QRS to end of U (Q-U) and (5) the P-R, QRS, and R-R intervals by standard definition.[14] The Q-T, Q-oT, and T intervals were corrected, as outlined by Lepeschkin and Surawicz,[12] using the formula of Bazett.[15]

Results

Electrolyte Changes. In terms of change from control levels expressed in milliequivalents per liter, the most pronounced variations after edathamil disodium (Na_2 EDTA) administration occurred in plasma calcium and plasma sodium (fig. 1). The electrolyte changes produced by edathamil calcium-disodium (Ca Na_2 EDTA) (the calcium salt) were insignificant, except possibly in the case of potassium.

With the administration of Na_2 EDTA, plasma calcium values dropped from 1.0 to 1.7 mEq. per liter below their control values with the lowest point at the end or shortly after the completion of the infusion. This represents a mean percentile change of 31.4. Return toward normal was gradual, usually beginning within 15 minutes after completion of the infusion.

In all cases, plasma potassium fell below the control value by 0.1 to 0.5 mEq. per liter. There was no apparent correlation between the degree of depression of plasma calcium and that of plasma potassium. It is unlikely that the fall in potassium is directly related to the induction of hypocalcemia by Na_2 EDTA since it occurs following the administration of Ca Na_2 EDTA as well.

Phosphate levels showed a more gradual fall and a more prolonged depression with a tendency to show a late rise above the control value. The absolute change was between 0.3 to 0.5 mEq. per liter below the control value. These same changes have been noted in patients similarly treated except that normal saline was substituted for edathamil solutions,[16] so this effect is probably independent of edathamil.

There was some variable rise in sodium values (1.0 to 8.0 mEq. per liter, or a mean percentile change of 2.9 per cent), probably related to the nature of the chelating salt and the vehicle used. In general, this rise reached its peak during the infusion or within 30 minutes following. No changes have been recognized in the electrocardiogram due to changes in the sodium ion concentration.[9] The change produced in the plasma sodium concentration of these subjects is small and is present in the control subjects; thus, it is felt that the electrocardiographic changes described in this study are entirely related to the changes in the calcium ion concentration.

Reynolds[9] also reported no changes in the electrocardiogram with variation in magnesium ion concentration. Another investigator[17] failed to demonstrate significant changes in serum levels of magnesium, calcium, pH, sodium and copper, following the administration of Ca Na_2 EDTA. Plasma magnesium and blood pH determinations were not done in the present study.

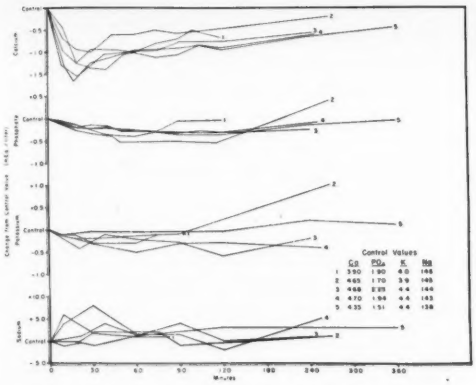

FIG. 1. The change from control values of plasma calcium, phosphate, potassium and sodium during and following the intravenous administration of edathamil disodium (Na_2 EDTA).

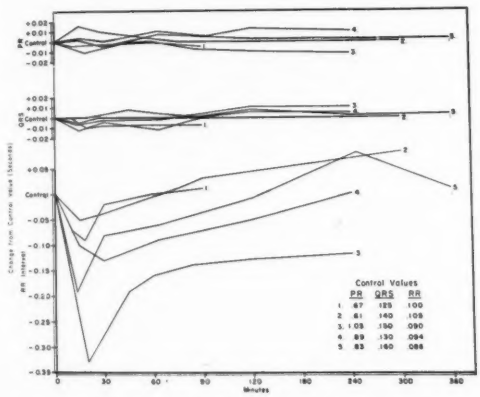

FIG. 2. The change from control values of P-R, QRS, and R-R intervals during and following the intravenous administration of edathamil disodium (Na_2 EDTA).

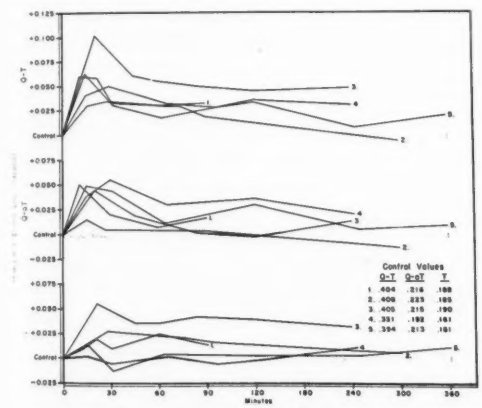

FIG. 3. The change from control values of Q-T, Q-oT, and T intervals during and following the intravenous administration of edathamil disodium (Na_2 EDTA).

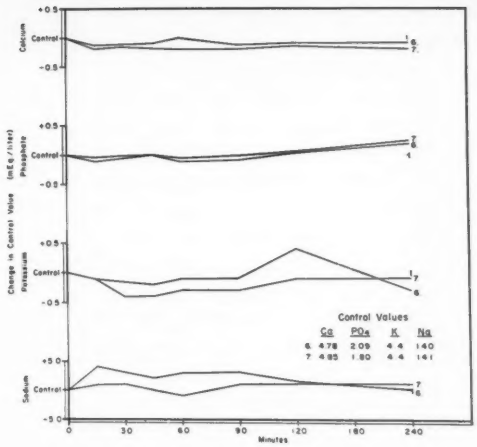

FIG. 4. The change from control values of plasma calcium, phosphate, potassium and sodium during and following the intravenous administration of edathamil calcium-disodium (Ca Na_2 EDTA).

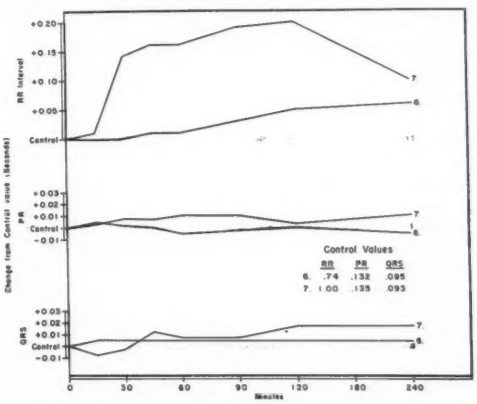

FIG. 5. The change from control values of R-R, P-R, and QRS intervals during and following the intravenous administration of edathamil calcium-disodium (Ca Na_2 EDTA).

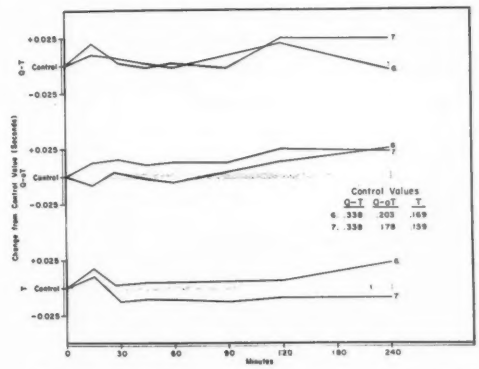

FIG. 6. The change from control values of the Q-T, Q-oT and T intervals during and following the intravenous administration of edathamil calcium-disodium (Ca Na_2 EDTA).

Subjective Changes. No symptoms appeared during the infusion of Ca Na_2 EDTA. All five subjects who received Na_2 EDTA developed mild symptoms, usually beginning within two or three minutes after starting the intravenous infusion. Aching, cramping pain developed along the course of the vein through which the infusion was given. This was apparently of muscular origin and was readily relieved by light local massage, but immediately reappeared as massage was stopped. A fine, generalized muscular tremor appeared during the infusion in all cases but lasted only two to five minutes. Numbness and tingling were present in the hands, lips, and occasionally the feet. All subjective symptoms subsided with completion of the infusion or within 10 minutes following infusion.

Changes in the Amplitude and Contour of the Electrocardiogram. During the infusion of Na_2 EDTA there was a general trend for the P, QRS and T complexes to become slightly reduced in amplitude. These changes were very small and generally less than 1 mm. (standardization of 10 mm. equals 1 mv.). No RS-T segment shift occurred with the edathamil disodium, but in one of the two subjects receiving Ca Na_2 EDTA there was an unexplained decrease in the amplitude of the QRS (over 2 mm.) and T (1.8 mm.) with S-T segment depression (0.5 mm.) at 240 minutes only. No other changes were noted with the infusion of Ca Na_2 EDTA.

Spatial vector analysis revealed no significant changes in the electric axis of the various electrocardiographic waves. It is felt, therefore, that these changes in amplitude are not due to a change in the electric axis of the P, QRS, T or S-T segment.

TABLE 1.—*Correlations Between the Change in Plasma Calcium and the Change in the Electrocardiographic Intervals*

Interval	Correlation Coefficient	p
R-R	+0.78	<0.01
Q-oT	−0.69	<0.02
Q-T	−0.76	<0.01
T	−0.21	>0.5

No dramatic changes were seen in the contour of the electrocardiogram. No inversion of T waves was encountered. In some instances there was a tendency for the beginning of the T wave to become blended into the RS-T segment. This was particularly true if there was slight S-T segment elevation present in the control precordial leads. The effect of this change was to make exact measurement of the beginning of the T wave very difficult, thus making the accurate measurement of Q-oT problematic. Since measurement of the interval Q-oT (length of the S-T segment) and the beginning of the T wave cannot be accurately determined in all cases, one cannot be certain that the RS-T segment is the interval primarily lengthened by hypocalcemia. Indeed, in this study, statistical analysis fails to reveal that the Q-oT is lengthened significantly more than the Q-T as the serum calcium falls ($p > 0.1$).

Changes in the Intervals of the Electrocardiogram. Prolongation of the Q-T and the Q-oT intervals has been observed by many previous investigators in the presence of hypocalcemia, but changes in the R-R interval have not been reported to occur. In this study marked changes occurred in the R-R, the Q-T, and the Q-oT intervals. The R-R interval was shortened (fig. 2); the Q-T, and the Q-oT intervals were prolonged (fig. 3). The reduction in R-R interval and the prolongation of Q-T and Q-oT intervals were proportional to the degree of hypocalcemia. In contrast, in the two subjects receiving edathamil calcium-disodium, there was no change in one and a prolongation in the R-R interval of the other (figs. 5 and 6).

These changes are statistically significant, and the close correlation of the degree of the changes in intervals with the absolute fall in serum calcium makes other factors, such as anxiety, much less probable causes of the effects seen (table 1).

The P-R interval showed no consistent nor appreciable change.

The QRS interval was consistently shortened during the period of infusion, but this was not correlated with the degree of hypocalcemia nor was it great enough to be of

definite significance (less than 0.01 second change).

The difficulties in measurement of the Q-T intervals and the misinterpretation of the Q-U interval for the Q-T interval has been emphasized by several authors[8, 9, 11, 18] who have suggested the use of multiple leads as utilized in this study as an aid in preventing this error. In the present study attempts in measurement of the Q-U interval were not always successful, since the shortened R-R interval caused the U wave (which was present, though small, in all control tracings) to be superimposed upon the following P wave, thus making measurements inaccurate. In those subjects in which the Q-U interval could be measured the change was generally less than 0.04 second prolongation.

Summary

1. The electrocardiographic effects of hypocalcemia produced by intravenously administered edathamil disodium have been studied in normal subjects.

2. The major changes noted with the production of hypocalcemia have been: shortening of the R-R interval and prolongation of the Q-oT and Q-T intervals, all proportional to the degree of hypocalcemia.

3. Other changes noted to occur, but minor in degree or not well correlated with the fall in serum calcium, were: slight reduction in amplitude of the P, QRS, and T; merging of the RS-T segment and the ascending limb of the T wave; shortening of the QRS interval; and Q-U and T interval prolongation.

4. No change in spatial P, QRS, and T vectors occurred with hypocalcemia.

5. No T wave flattening or T wave inversion, and no elevation or depression of the RS-T segment appeared.

Acknowledgment

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Summario in Interlingua

In le passato il non esseva possibile studiar le effectos electrocardiographic de hypocalcemia in subjectos normal. Edathamil-dinatrium es un potente agente chelative con un forte affinitate pro calcium ionic quando illo es administrate intravenosemente. Iste agente esseva usate pro producer hypocalcemia in subjectos normal de maniera que studiar le effectos electrocardiographic deveniva possibile. Le major alterationes producite in le electrocardiogramma per le induction de hypocalcemia esseva reduction del intervallo R-R e prolongation del intervallos RS-T e Q-T, omnes proportional al grado de hypocalcemia. Nulle alteration del spatial vectores P, QRS, e T, nulle applattation o inversion del unda T, e nulle elevation o depression del segmento RS-T se manifestava in association con hypocalcemia.

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Coarctation of the Aorta Associated with Patent Ductus Arteriosus

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The combination of patent ductus arteriosus and coarctation of the aorta poses special anatomic, physiologic and surgical problems. An experience with 14 such cases is presented, which suggests that pulmonary hypertension occurs frequently in these cases. Physiologic data in cases having coarctation of the aorta, patent ductus arteriosus and pulmonary hypertension that underwent cardiac catheterization are presented. Clinical, anatomic, physiologic and surgical implications of this combination are discussed.

THE combination of coarctation of the aorta and patent ductus arteriosus may present certain special problems in surgical management. In order to survey critically the challenge posed by these relatively uncommon cases, the surgical experience with them at the Mayo Clinic has been reviewed.

Historically, the combination of coarctation of the aorta and patent ductus arteriosus has been recognized for more than a century. Craigie, in 1841,[1] was one of the first to describe a case having these 2 anomalies. In 1862 de Almagro[2] described a similar patient who died at the age of 19 years of a cerebrovascular accident. Other patients were recorded by Legg[3] in 1878, Horder[4] in 1908 and Staunig[5] in 1913. These latter 3 patients all died of rupture of the aorta. Maude Abbott,[6] in an extensive review of the literature on coarctation of the aorta in 1928, found that 10 per cent of 200 patients having this anomaly had an associated patency of the ductus arteriosus. Of these 200, only 21 were diagnosed ante mortem as having coarctation, while seven others were considered to have "obstruction of the aorta." In no instance was the association of a patent ductus arteriosus with the coarctation diagnosed ante mortem. In the last decade, with the advent of increased clinical acumen, reconstructive curative surgery, and development of new diagnostic technics, the two associated conditions have been diagnosed preoperatively and effectively treated surgically.

The records of 193 cases in which coarctation of the aorta was treated surgically at the Mayo Clinic were reviewed. In 14 instances (7.3 per cent of cases), the ductus arteriosus was grossly patent. A similar figure was given by Gross [7] in a review of 100 cases of coarctation of the aorta in 1950. He noted that the ductus arteriosus was patent in seven instances. Other reported instances of this combination include case reports by Swan and associates[8] in 1949, Taylor and associates[9] in 1950 and Leeds and associates[10] in 1953. Edwards and associates,[11, 12] in several earlier communications from the Mayo Clinic, emphasized that increased pulmonary vascular resistance could occur with the combination of coarctation of the aorta and patent ductus arteriosus. They were able to correlate this occurrence of increased pulmonary vascular resistance with anatomic changes in the pulmonary vessels, demonstrated at necropsy. One of our cases was previously reviewed in detail by them.[11]

CLASSIFICATION OF CASES

For many years, classification of coarctation of the aorta has been based primarily on the site at which the ductus arteriosus, whether patent or ligamentous, is attached to the aorta. This idea was first suggested by Bonnet in 1903. He felt that in those cases in which the ligamentum arteriosum inserted proximal

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to the coarctation, the lesion should be called "adult," while in those cases with a hypoplastic aortic arch and a ligamentum arteriosum inserting distal to the coarctated segment, the lesion should be called "infantile." Johnson and associates,[13] in an excellent paper on this subject, enlarged this classification to include not only the location of the ductus with respect to the coarctation, but also whether or not collateral circulation was present. They felt that if the ductus was located proximal to the coarctation, collateral circulation was necessary to maintain life. If the ductus was distal to the coarctation, however, the amount of blood flowing from the pulmonary artery into the distal portion of the aorta would be determined by the comparative pressure of the collateral circulation and that of the pulmonary artery.

The experience at the Mayo Clinic with 14 cases of coarctation of the aorta associated with patent ductus arteriosus suggests that an important feature of this combination of defects is the presence or absence of pulmonary hypertension. The association of pulmonary hypertension with patent ductus arteriosus and coarctation of the aorta has been discussed previously from this institution.[9, 11, 12] The 14 cases of associated coarctation of the aorta and patent ductus arteriosus in this study have been divided into two groups: coarctation associated with patent ductus arteriosus, pulmonary hypertension and increased pulmonary resistance; and coarctation associated with patent ductus arteriosus but with normal pulmonary resistance. For these purposes, pulmonary hypertension is defined as an average pressure in the pulmonary artery in excess of 40 mm. Hg systolic, and increased pulmonary resistance represents a resistance in excess of 200 dynes sec. cm.$^{-5}$.

In this series, the occurrence of patency of the ductus arteriosus without pulmonary hypertension posed only slight additional problems in the treatment of coarctation of the aorta. A patent ductus arteriosus associated with pulmonary hypertension, however, added considerably to the technical problems of operation in coarctation. It seemed of secondary importance, surgically, whether the patent ductus attached to the aorta in the coarctated area, above it or below it.

Clinical Data

In eight patients patent ductus arteriosus was found at operation to be associated with coarctation of the aorta in the absence of pulmonary hypertension. In six of these patients the ductus entered the aorta proximal to the coarctation while in one patient the ductus entered opposite and in another distal to it. Seven of these eight patients had well-developed collateral circulation. There was one postoperative death in this group.

Six patients had patent ductus arteriosus associated with aortic coarctation and acceptable evidence of pulmonary hypertension. The ages of the patients in this group varied between 20 months and 27 years. In 1 of the 6 patients with coarctation, patent ductus arteriosus and pulmonary hypertension, the ductus was divided but the coarctation was not resected. In the five cases in which a complete repair was done, there were two postoperative deaths.

The location of the ductus with respect to the coarctation was different in the cases in which pulmonary hypertension was present from those in which the pulmonary pressure was normal. While 6 of the 8 patients in the group without pulmonary hypertension had a ductus joining the aorta proximal to the coarctation, 1 of the 6 in the pulmonary hypertension group had a ductus joining the aorta proximal to the coarctation, while in three the ductus arteriosus entered exactly at the coarctation and in two it entered the aorta distal to the coarctation. Table 1 includes a summary of the clinical data in these six cases in which pulmonary hypertension was present.

Physiologic Data

In only 4 of the 6 patients with pulmonary hypertension were preoperative catheterization data available (table 2). In the other 2 cases, acceptable evidence of severe pulmonary hypertension was obtained at opera-

TABLE 1.—*Clinical Data on 6 Patients with Coarctation of the Aorta, Patent Ductus Arteriosus, and Pulmonary Hypertension*

Case	Age	Sex	Anatomy	Shunts (by catheterization)	Operative procedure	Result
1	4 yr.	M	Ductus at coarctation, poor collateral circulation	On air: R → L and L → R On O_2: L → R only	Ductus divided, coarctation resected	Died several hours postoperatively
2	27 yr.	M	Ductus proximal to coarctation, good collateral circulation	On air: L → R only No oxygen studies	Ductus divided, coarctation resected	Good
3	12 yr.	M	Ductus at coarctation, poor collateral circulation	On air: R → L and L → R On O_2: L → R only	Ductus divided, coarctation resected	Good, regression, pulmonary hypertension
4	20 mo.	F	Ductus at coarctation, poor collateral circulation	On air: R → L On O_2: L → R	Ductus divided, coarctation resected	Good
5	16 yr.	M	Ductus distal to coarctation	No catheterization data	Ductus divided, coarctation not resected	Fair
6	7 yr.	F	Ductus distal to coarctation, poor collateral circulaton	No catheterization data	Ductus divided, coarctation resected	Died suddenly on thirteenth postoperative day

TABLE 2.—*Physiologic Data from Cardiac Catheterization on 4 Patients with Coarctation of the Aorta, Patent Ductus Arteriosus, and Pulmonary Hypertension*

Case	Pressure, mm. Hg					Flow, L./min.				Shunts, %			
	Femoral artery	Radial artery	Right ventricle	Pulmonary trunk	Wedge	Pulmonary		Systemic		R → L		L → R	
						Air	O_2	Air	O_2	Air	O_2	Air	O_2
1*	67/53	L.: 65/53 R.: 95/58	98/8	92/66	35/22	—	—	—	—	20†	0	30	54
2	109/77	182/70	61/13	61/41	—	8.2	—	4.2	—	0	—	50	—
3*	115/63	140/50	109/7	106/68	30/20	7.9	41‡	3.5	2.9	20	0	57	92‡
4*	59/46	110/68	124/8	131/77	—	1.6	2.6	1.6	1.9	6	0	0	30

* Catheterized under general anesthesia.

† Descending aorta.

‡ These values for pulmonary blood flow and left → right shunt are subject to large error, since they are based on an arteriovenous difference of only 0.5 volume per cent.

tion by the surgeon's noting a very tense pulmonary artery in which the pressure seemed equal to that in the aorta. In 2 of the 4 patients who underwent cardiac catheterization, the pulmonary artery pressure was as high as or higher than the aortic pressure above the coarctation. The ages of these patients were 4 years and 20 months, respectively. In both cases, there was right-to-left shunting of blood across the ductus arteriosus when the patients were breathing room air, and associated desaturation of blood in the descending aorta. No such right-to-left shunting was present when the patients were breathing 100 per cent oxygen, however. Left-to-right shunting of blood was present in only one of these cases on room air and in both cases on oxygen.

Two of the four patients, ages 12 and 27 years, respectively, had pulmonary artery pressures lower than those of the aorta above the coarctation, one being 61/41 mm. Hg and the other 106/68 mm. Hg. This latter patient had right-to-left shunting of blood across the patent ductus when breathing air but no right-to-left shunt when breathing oxygen, while the former patient had no right-

TABLE 3.—*Pulmonary and Systemic Vascular Resistances in Four Cases of Patent Ductus Arteriosus, Coarctation of the Aorta, and Pulmonary Hypertension in Which Cardiac Catheterization Was Performed*

Case	Total pulmonary resistance, dynes sec. cm.$^{-5}$		Total systemic resistance, dynes sec. cm.$^{-5}$	
	Air	O_2	Air	O_2
1	774*	662	1,362*	1,075
2	468	—	2,035	—
3	860	150	2,240	2,615
4	4,750	1,261	4,100	3,960

* An assumed oxygen uptake was used for the calculation of pulmonary and systemic blood flow in this case.

to-left shunt or aortic desaturation. Both patients had a left-to-right shunt, the latter one having a 92 per cent* shunt in this direction when breathing oxygen.

Direct femoral artery pressures were measured preoperatively in all four patients who were catheterized. In each instance these pressures were considerably lower than simultaneous radial pressures (table 2).

Pulmonary and systemic flow calculations employing the Fick principle were carried out with the patient breathing in sequence air and oxygen in 2 of these 4 catheterized patients, and in a third patient with the patient breathing air only. Table 2 includes the amount of flow calculated. These flows reflect the decrease in pulmonary resistance and increase in left-to-right shunting of blood across the ductus and into the pulmonary circulation that occurs when the patient breathes oxygen. The calculation of the total pulmonary resistance and total systemic resistance was carried out on the four patients who were catheterized preoperatively. These data are included in table 3.

One of the four cases has been reviewed in detail recently by Shepherd and associates.[14] They found the total pulmonary resistance to be 860 dynes sec. cm.$^{-5}$ preoperatively. It could be reduced to 150 dynes sec. cm.$^{-5}$ with the patient breathing 99.6 per cent oxygen. The pulmonary arteriolar resistance on air was also markedly elevated, being 620 dynes sec. cm.$^{-5}$ Four months postoperatively, this patient was again catheterized. His excellent clinical result was reflected in the postoperative catheterization findings. Table 4 gives a brief résumé of these findings. It is to be noted that right ventricular pressure fell from a preoperative level of 109/7 to 59/3 mm. Hg postoperatively, while the pulmonary arterial "wedge" pressure fell from 30/20 to 17/11 mm. Hg. Similarly, the total pulmonary resistance fell in 4 months after operation to 596 dynes sec. cm.$^{-5}$ Pulmonary arteriolar resistance fell postoperatively, being 372 dynes sec. cm.$^{-5}$ This patient was clinically well and had completely recovered from the effects of operation.

* This value is subject to large error, since it is based on an arteriovenous difference of only 0.5 volume per cent.

RESULTS OF OPERATION

The results of operation in the group of eight patients having a patent ductus arteriosus associated with coarctation of the aorta and no pulmonary hypertension were good in every case except for the one postoperative death. Of the six patients having pulmonary hypertension, patent ductus and coarctation of the aorta, two died in the postoperative period. Of the four patients surviving operation, three had good results with adequate lowering of the systemic blood pressure. One of these underwent cardiac catheterization preoperatively and postoperatively, as previously indicated. One patient, however, had only a fair result—the one in whom the ductus was divided without repair of the coarctation.

ANATOMIC AND PHYSIOLOGIC FEATURES

In this group of 14 cases of combined defects the physiologic and the anatomic patterns seemed related. An endeavor was therefore made to classify each case according to the point of attachment of the patent ductus arteriosus and the aorta with reference to the coarctation. In several cases this was difficult to determine and required microscopic study for accurate classification.* Three different insertions of the patent ductus were recognized: proximal to the coarctation, at or

* We are indebted to Dr. J. E. Edwards for assistance in this regard.

TABLE 4.—*Comparison of Preoperative and Postoperative Data on Case 3 from Cardiac Catheterization*

	Pressure, mm. Hg					Resistance, dynes sec. cm.$^{-5}$		
	Pulmonary trunk	Right ventricle	Wedge	Radial artery	Femoral artery	Total pulmonary		Pulmonary arteriolar, air
						Air	O_2	
Preoperative	106/68	109/7	30/20	140/50	115/63	860	150	620
Postoperative	51/13	59/3	17/11	137/75	133/80	596	507	372

opposite the coarctation, and distal to the coarctation.

When the patent ductus inserted proximal to the point of coarctation, a left-to-right shunt from the aorta to the pulmonary artery was usual. This shunt was suspected in all seven of the patients with this anatomic arrangement, although it was confirmed only in the one patient who was catheterized preoperatively. Pulmonary hypertension and increased pulmonary vascular resistance were rarely found when the ductus inserted proximal to the coarctation. Only 1 of 7 patients in this category had pulmonary hypertension and this patient had no right-to-left shunt.

When the patent ductus inserted at or opposite the coarctation, a different physiologic pattern occurred. Four of the patients had this anatomic arrangement. In three of these (cases 1, 3 and 4) pulmonary hypertension and increased pulmonary resistance were demonstrated at cardiac catheterization. The other patient was not catheterized, but the surgeon noted evidence of pulmonary hypertension. All of the patients in this group studied by cardiac catherization had bidirectional shunts. In those cases in which the ductus inserted opposite the coarctation, the aortic obstruction seemed less marked than in the usual case of coarctation (table 2). In this connection all four patients having this anatomic arrangement had little or no collateral circulation. It is probable that the ductus acts as a detour, blood flowing from the proximal portion of the aorta into the aortic end of the ductus, around the coarctation, and thence from the ductus into the distal portion of the aorta.

When the patent ductus inserted distal to the coarctation, the physiologic situation was somewhat different. In one of the patients, the coarctation was not severe and there was considerable flow directly down the aorta with little collateral circulation. This patient also had pulmonary hypertension as judged by the surgeon and was the only patient in whom resection of the coarctation was not carried out, although the ductus was divided (case 5). In another case in which the ductus inserted below the coarctation, there were severe coarctation, minimal collateral circulation and pulmonary hypertension. Although cardiac catheterization had not been done to settle the point, it is probable that the ductus was supplying a portion of the descending aortic blood. In a third case with the ductus inserting below the coarctation, there was good collateral circulation and no pulmonary hypertension. Although cardiac catheterization was not carried out, presumably this patient had a left-to-right shunt supplied by the collateral circulation to the pulmonary artery. From these examples it is apparent that the flow of blood down the descending aorta in patients in whom the ductus inserts below the coarctation is governed by several factors: the caliber of the aortic lumen at the coarctation, the status of pulmonary resistance, and the development of the collateral circulation.

CLINICAL CONSIDERATIONS

Significant in a discussion of the surgical aspects of patients with patent ductus arteriosus and coarctation of aorta is the fact that 6 of 14 such patients had pulmonary hypertension and that of the 5 patients with pulmonary hypertension in whom the combined defect was completely repaired two died in the postoperative period. One death occurred within a few hours of operation. In this 4 year old child the wedge pressure had been elevated at the time of cardiac catherization. At necropsy, mitral insufficiency and endocardial sclerosis of the left ventricle were

found. All suture lines were intact. The other hospital death occurred suddenly, 13 days after operation. Necropsy did not reveal the cause of death in this case.

In instances of severe pulmonary hypertension and attachment of the ductus in the region of the coarctation or distal to it, considerable amounts of the blood going into the descending aorta may be coming from the pulmonary artery, as already mentioned. The usually rich collateral circulation is sometimes poorly developed under these circumstances. Then cross-clamping of the aorta for a period long enough to allow an aortic resection and anastomosis might theoretically cause paralysis of the lower limbs. This catastrophe has not occurred in any of the cases in this series. Because of this theoretic possibility, however, the anastomosis is made with as much dispatch as possible. In the last case in which operation was performed, moderate hypothermia was utilized for protection of the spinal cord during the operation as suggested by De Bakey and Cooley.[15]

Another fact concerning this group of patients may be of importance in the postoperative management, namely, that high oxygen concentrations lower the pulmonary artery pressure in most people with pulmonary hypertension associated with congenital heart disease. For this reason, the patient is kept under high oxygen concentrations for a prolonged period after operation, in some instances 7 to 10 days. Though this maneuver is on an empiric basis, it may lower the pulmonary artery pressure enough to take some of the strain off the right ventricle during this critical period.

Obviously, since the technical problems of dividing the ductus in a patient with a tense, often thin pulmonary artery are great, care must be taken during the procedure itself. It is of value, after the dissection has been entirely completed, to plan the rest of the operation carefully. It is usually best to place the occluding clamp on the ductus in such a position that there is a small but definite space between it and the pulmonary artery. The aorta can be cross-clamped in the usual fashion for resection of the coarctation and divided above and below the coarctated area. This procedure leaves the coarctated portion of the aorta attached to the patent ductus arteriosus. After completing the end-to-end aortic anastomosis in the usual fashion and opening the anastomosis, one can trim away enough of the coarctated portion of the aorta so that the patent ductus is left in a condition suitable for closure. In this way, an adequate cuff for one row of fine interrupted silk sutures is left and a satisfactory closure can be obtained.

Summary

The association of a patent ductus arteriosus with coarctation of the aorta has occurred in about seven per cent of cases of coarctation of the aorta in which surgical treatment was used. In many cases the patency of the ductus arteriosus is small and unimportant physiologically and is discovered at the operating table. This group presents little trouble, either technically or prognostically to the surgeon. The group in which a patent ductus arteriosus is associated with pulmonary hypertension, however, is important to recognize preoperatively, both because of the greater risk of operation and because of the guarded early and late prognosis.

The pathologic physiology, surgical technic, and postoperative care of the patient with coarctation, patent ductus, and pulmonary hypertension are discussed.

Summario in Interlingua

Le association de patente ducto arteriose con coarctation del aorta occurreva in circa 7 pro cento del casos de coarctation del aorta in que un operation chirurgic esseva effectuate. In multe casos le patentia del ducto arteriose es pauco extense e sin importantia physiologic de maniera que illo es discoperite solmente durante le operation. Iste gruppo de casos presenta al chirurgo nulle extraordinari problemas technic o prognostic. Tamen, le gruppo de casos in que un patente ducto arteriose es associate con hypertension pulmonar implica plus grande riscos operatori e require un plus alte grado de circumspection in le prognose tanto immediate

como etiam a longe durantia de maniera que lor recognition ante le operation deveni un desiderato multo importante.

Es discutite le physiologia pathologic, le technica chirurgic, e le maneamento post-operatori de patientes con coarctation, patente ducto arteriose, e hypertension pulmonar.

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The Effect of Hyperventilation on the Normal Adult Electrocardiogram

By R. H. WASSERBURGER, M.D., K. L. SIEBECKER, JR., M.D., AND W. C. LEWIS, M.D.

With the technical assistance of C. Janet Lloyd

The effect of brief hyperventilation on the precordial T waves of 350 normal adults is described. Evidence is presented that brief hyperventilation initiates a vagal reflex which results in the T-wave inversion. Supportive data are also given to exclude respiratory alkalosis as a possible mechanism. Caution is advised in interpreting isolated T-wave inversions as indicative of organic heart disease. It is proposed that isolated T-wave inversion be deleted as a criterion for a "positive" exercise test.

TRANSIENT or persistent T-wave inversions in the left and midprecordial unipolar leads have been observed in approximately 10 per cent of apparently healthy, adult Negro males and less commonly in Caucasian adults.[1, 2] This pattern is known as the "juvenile pattern" because of its resemblance to the T-wave changes observed in infants and young children. The clinical importance of these electrocardiographic changes lies in the similarity to those of organic heart disease.

Previous reports showed that the T-wave inversions could be abolished by the oral administration of potassium salts or by propantheline bromide (Pro-Banthine, Searle) given intravenously.[1, 2] Hyperventilation, on the other hand, intensified the precordial T-wave inversions and, when the T-wave had transiently become upright, elicited the originally observed T-wave changes.

These observations with hyperventilation prompted a study of the electrocardiographic effects of hyperventilation on a number of adult patients who had normal resting electrocardiograms. In addition, the effects of breathing various concentrations of carbon dioxide and oxygen were investigated to determine whether the observed T-wave changes were due to respiratory alkalosis. The effects of the vagal blocking agent, Pro-Banthine, and the potassium ion in abolishing the hyperventilation effect were once again studied. The patients were also evaluated from the emotional standpoint, inasmuch as it has been established[1, 2] that the patients exhibiting the overt "juvenile electrocardiographic pattern" were tense, immature, and often neurotic.

MATERIALS AND METHODS

Electrocardiograms were taken of 901 patients in the Veterans Administration Hospital, Madison, Wis., between Jan. 1, 1954 and Sept. 30, 1955. Of this total, 350 patients were selected for inclusion in this study on the basis of the following criteria: (1) the presence of a normal resting electrocardiogram, (2) absence of debility, (3) an age range between 18 and 50 years and (4) no clinical evidence of coronary artery or significant cardiovascular disease. Of this group, there were 258 Caucasians and 92 Negroes; the mean age was 35 years.

All electrocardiograms were taken in recumbency, with a direct-writing machine. Hyperventilation consisted of 10 to 15 seconds of forced, rapid respiration that was repeated during the recording of each precordial unipolar lead. The patients exhibiting the most marked T-wave changes during hyperventilation (positive reactors) were subjected to the following additional studies:

1. *Hyperventilation during Inhalation of Various Gaseous Mixtures*

Six patients with the most striking T-wave inversion following hyperventilation were observed during the inhalation of various gaseous mixtures containing low, normal, and high concentrations of oxygen and carbon dioxide. Hyperventilation was

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An abstract of the preliminary phases of this study (Wasserburger, R. H., and Lorenz, T. H.: An electrocardiographic pitfall—"the juvenile pattern.") appeared in Circulation **12**: 787, 1955.

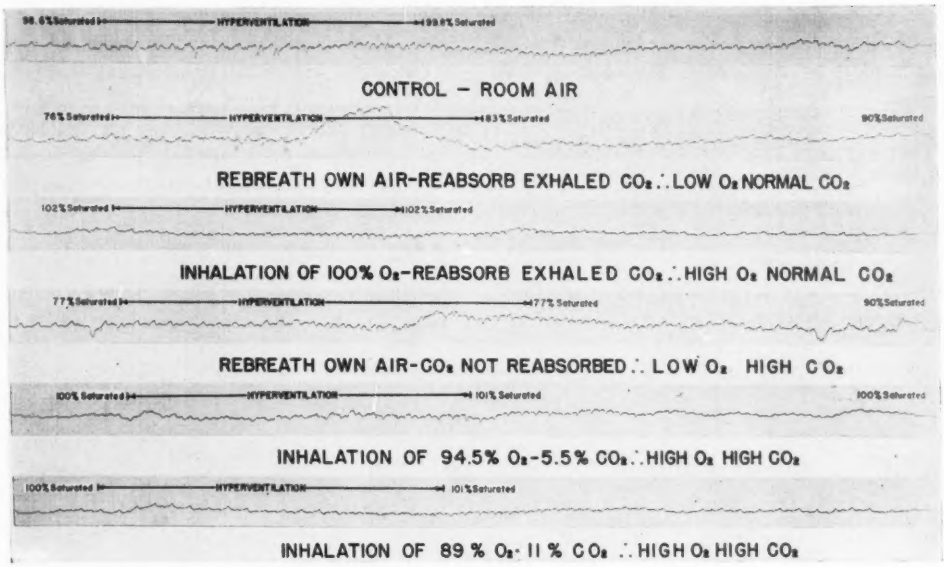

FIG. 1. Lead V_4 electrocardiogram during complete hyperventilation study on L. M., 32 year old Negro. The percentages refer to oxygen saturation. The control tracing, with patient breathing room air, showed a very active hyperventilation reflex with marked T-wave inversion within 8 seconds. This effect persisted while the patient breathed low O_2, normal CO_2; high O_2, normal CO_2; low O_2, high CO_2; and high O_2, high CO_2. The T-wave inversion patterns during the inhalation of excessive CO_2 (11 per cent) were shorter than those seen on previous studies.

repeated during the inhalation of each of the 4 gaseous mixtures. The unipolar leads with the most marked T-wave changes during the control hyperventilation were recorded during the administration of the gaseous mixtures. Continuous monitoring with a Waters-Conley ear oximeter was carried out during the period of gas administration to detect changes in arterial saturation. Arterial blood pH, pCO_2 and venous blood potassium concentrations were not measured.

2. *Vagal Blockade*

The effect of a vagal blocking agent, Pro-Banthine, in abolishing the hyperventilation effect was studied in 11 instances. Pro-Banthine, (30 mg. diluted in 10 ml. of water) was administered intravenously in increments of 5 mg. over a 3 to 4 minute period. The endpoint of drug administration was tachycardia of 140 to 150 beats per minute. Hyperventilation was subsequently repeated during maximal Pro-Banthine activity, usually 45 to 90 minutes following the injection, when the drug-induced tachycardia had stabilized at 125 to 130 beats per minute.

. *Potassium Salts*

The effect of 10 Gm. of orally administered potassium salts, (5 Gm. of potassium bicarbonate and 5 Gm. of potassium acetate, diluted in 30 ml. of water) in abolishing the electrocardiographic effect of hyperventilation was likewise studied in six instances. Hyperventilation was repeated 30 to 60 minutes after ingestion of potassium, the period of maximal drug effect.

4. *Psychiatric Evaluation*

Twelve patients had previously been referred for psychiatric consultation and 11 additional patients were available for psychiatric study when the evaluation of the emotional factors were undertaken. Twenty-five patients had completed the Madison Sentence Completion Form[3] (a test method designed specifically to evaluate the attitudes and emotional reactions of patients with tuberculosis). Therefore, all patients in this study had either psychologic testing or psychiatric evaluation, and many had both. During the individual standardized psychiatric interviews, emphasis was placed on the patient's personality structure, maturity, and reactions to emotional stress.

RESULTS

T-wave inversions were observed in 37 of the 350 patients tested by hyperventilation. The T-wave changes were observed in two or more of the mid and left precordial leads. Twenty-five were Caucasians and 12 were

Negroes (9.5 and 13 per cent, respectively). The mean age of the positive reactors was 32 years and was similar in Caucasians and Negroes.

1. *Hyperventilation during Inhalation of Various Gaseous Mixtures*

Regardless of the inhaled gaseous concentration, persistent T-wave inversion was observed upon brief hyperventilation in the 6 patients studied. The T-wave inversion, however, that occurred during a period of inhalation of 89 per cent oxygen and 11 per cent carbon dioxide was of shorter duration. The effect of hyperventilation was not so great during this period, apparently because of the narcotizing effect of the high concentration of CO_2. Oxygen saturation increased uniformly during the period of hyperventilation in all gaseous atmospheres (fig. 1).

2. *Vagal Blockade*

Complete abolition of the hyperventilation effect by Pro-Banthine was observed in 8 of

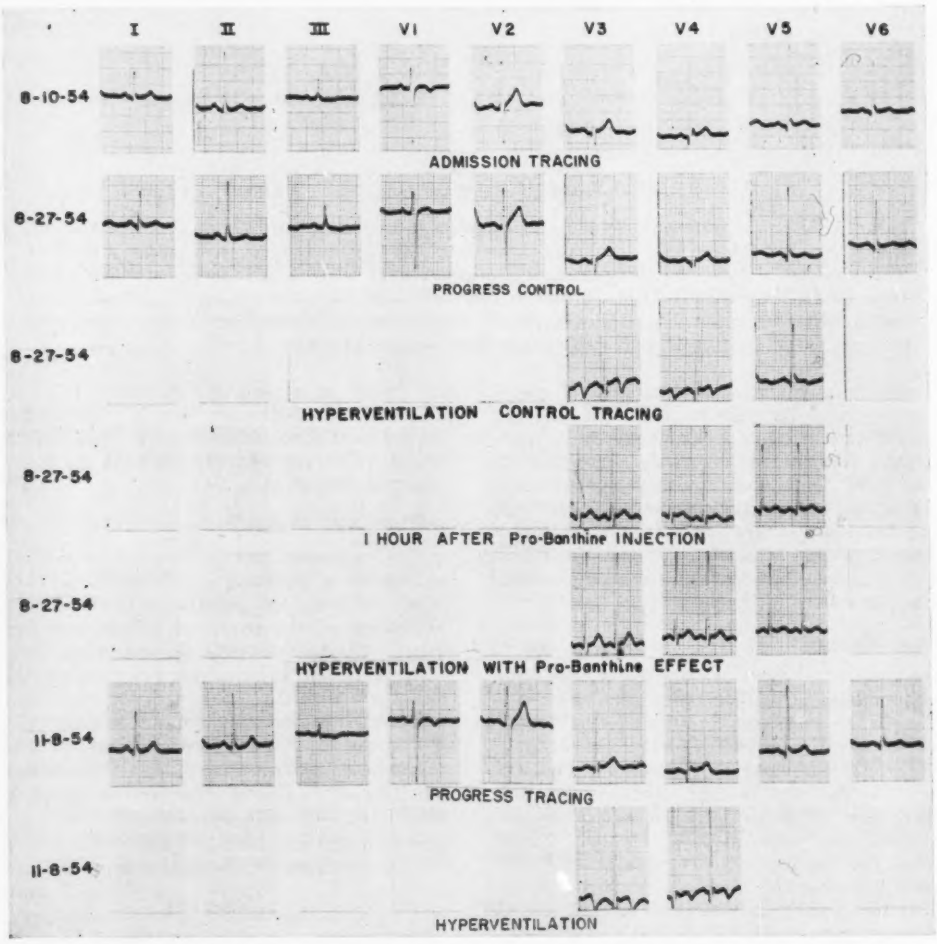

FIG. 2. A 26 year old Negro. Electrocardiograms on 8–10–54 and 8–27–54 were normal. Marked T-wave inversions, V_2 through V_5, followed hyperventilation and disappeared after Pro-Banthine. The tracing of 11–8–54 was normal and marked inversions of T waves in V_2 and V_4 followed hyperventilation.

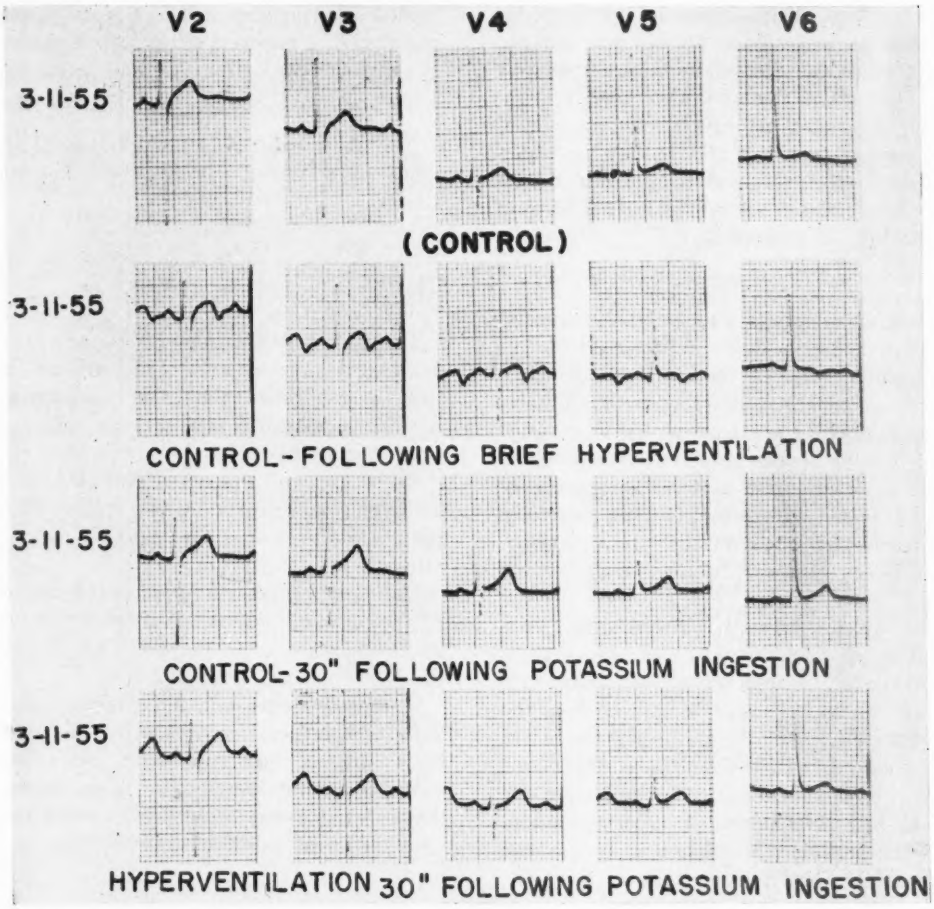

FIG. 3. W. W., a 22 year old Negro. Resting electrocardiogram of 3–11–55 was normal. Hyperventilation resulted in marked T-wave inversions except after the ingestion of potassium.

the 11 patients studied (fig. 2). One patient showed only partial blockade and two patients showed no change. In these two patients, only 5 mg. of Pro-Banthine were given because of marked tachycardia. Previous studies have indicated that at least 15 mg. are necessary to abolish the hyperventilation effect. There were no other untoward effects of Pro-Banthine.

3. *Potassium Salts*

The oral administration of potassium salts consistently abolished the hyperventilation reflex within 30 to 60 minutes in the 6 patients studied (fig. 3). There was no evidence of potassium toxicity.

4. *Psychiatric Evaluation*

The prevalence of autonomic instability, tension and anxiety and marked hypochondriac tendencies, found in our earlier series,[2] was confirmed in the present group of 37 patients. The patients were generally shy, passive-dependent and inhibited with marked inner tension. They showed an inability, or at least a marked disinclination, to express their feelings. Most had palmar hyperhidrosis, some dripped with sweat and many admitted extreme tension and palpitation during the interview. Diarrhea and frequency of urination were noted by a number of patients when

under tension. The unsuccessful nature of the patients' defense against anxiety was striking. Their relations with others had a distinctly immature flavor. Compulsive compliance was the most common method of handling aggressive feelings. It would appear that the "juvenile pattern" in the electrocardiogram has its emotional counterpart in a particular form of "juvenility" of personality.

Discussion

Much stress is placed on the diagnostic and prognostic significance of isolated T-wave inversions.[4-6] Indeed, one of the principal criteria of an abnormal exercise test is a reversal in polarity in the precordial T waves.[7-9] Such T-wave inversions have been observed as a benign "juvenile pattern" in apparently normal, young, Negro males. This pattern is nevertheless frequently misinterpreted as showing coronary, myocardial, or pericardial disease.

The overt "juvenile pattern" has been found in approximately 10 per cent of adult Negro males, though it is relatively rare among Caucasian males.[2] It appears from the present study that the pattern is latent in both Negro and Caucasian males. The latent form can be demonstrated by subjecting the patient to a brief period of hyperventilation. With this technic it was found in 13 per cent of the Negro and 9.5 per cent of the Caucasian patients.

It has been suggested that the T-wave inversions during hyperventilation were due to respiratory alkalosis.[10-14] The promptness with which the pattern follows initiation of hyperventilation and the appearance of the pattern during inhalation of high concentrations of CO_2 exclude this mechanism.

The hyperventilation effect may be explained as a vagal reflex arising in the thorax, similar to the Hering-Breuer reflex. Support is given to this concept by the blockade of the effect by Pro-Banthine or potassium.

Psychiatric evaluation of these patients showed them to be tense, immature, and emotionally disturbed. They expressed much inner hostility, yet exhibited external passivity, and they met stressful situations with compulsive compliance. The T wave therefore might well be regarded as the "stress segment" of the electrocardiogram.

Summary

The electrocardiograms of 350 normal adult males were studied following brief hyperventilation.

In 37 patients, T-wave inversions were observed in two or more of the precordial leads. This phenomenon is regarded as a latent "juvenile pattern."

Psychiatric evaluation of these patients revealed them to be tense, immature and emotionally disturbed. "Juvenility" is expressed in their personality structure as well as in their electrocardiogram.

Respiratory alkalosis was excluded as the underlying mechanism by observation of the pattern during forced breathing of high CO_2 atmospheres.

The hyperventilation effect is believed due to a vagal reflex. Support is given this concept by demonstration of the blocking effect of Pro-Banthine and potassium.

Caution is advised in interpreting isolated T-wave inversions as indicative of organic heart disease, particularly in emotionally disturbed, tense individuals. It is proposed that isolated T-wave inversion be deleted as a criterion for a "positive" exercise test.

Acknowledgment

The authors wish to express their appreciation to Forrest J. Fischer and Thomas L. Marlar for their valuable photographic assistance.

Summario in Interlingua

Le electrocardiogrammas de 350 normal adultos mascule esseva studiate post breve hyperventilation. In 37 subjectos, inversiones del unda T esseva observate in 2 o plus derivationes precordial. Iste phenomeno es considerate como un latente "configuration juvenil." Le evalutation psychiatric del subjectos revelava que illes esseva tense, immatur, e emotionalmente disturbate. "Juvenilitate" es manifeste in le structura de lor personalitate tanto ben como in lor electrocardiogramma. Alcalosis respiratori esseva excludite como mechanismo subjacente proque le configuration se

observava durante le respiration fortiate de aere a alte contento de CO_2. Le effecto del hyperventilation es debite in nostre opinion a un reflexo vagal. Iste conception es supportate per le demonstration de un effecto blocante de Pro-Banthina e kalium. Nos recommenda prudentia in interpretar isolate occurrentias de invertite undas T como indication de organic morbo cardiac, specialmente in tense e emotionalmente disturbate individuos. Nos propone que le occurrentia isolate de invertite undas T es supprimite como criterio de "positivitate" in tests de exercitio.

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Results of Prolonged Treatment with Pentolinium Tartrate

with Special Reference to the Addition of Rauwolfia, Hydralazine or Both

By EDWARD D. FREIS, M.D., AND ILSE M. WILSON, M.D.

A series of 96 patients with severe hypertension has been treated with pentolinium tartrate for an average period of 12 months. Seventeen patients died. Therapy was more effective in arresting changes in the optic fundi and in the heart than in the kidneys. Various combinations of hypotensive agents were tested and it was concluded that in general the combination of pentolinium tartrate, Rauwolfia and hydralazine resulted in the greatest reduction of blood pressure with the least degree of side effects due to ganglionic "blockade."

SOON after pentolinium tartrate was synthesized by Libman, Pain and Slack,[1] pharmacologic studies by Wein and Mason[2] indicated that it was a potent ganglionic blocking agent with a prolonged duration of action. Preliminary clinical results were reported by Campbell and Maxwell,[3] Smirk[4] and from this clinic.[5] These reports indicated that pentolinium tartrate was an orally effective, potent, antihypertensive drug that appeared to be useful in the treatment of patients with more severe, fixed types of hypertension. In the present report, the long-term experience with pentolinium tartrate both alone and in combination with certain other hypotensive agents is presented.

MATERIALS AND METHODS

The treatment group consisted of 96 patients selected because of severe, sustained hypertension (table 1). Their ages ranged from 27 to 65 years, with an average age of 47 years. All except 15 of these patients were hospitalized prior to or during the initiation of treatment with pentolinium. Prior to therapy, 56 per cent exhibited grade III or more changes in the optic fundi and 39 per cent had some degree of nitrogen retention.

Electrocardiograms were taken of 83 patients and 66 exhibited the pattern of left ventricular hypertrophy. Frank congestive heart failure was diagnosed in 13 of the patients, although lesser degrees of cardiac decompensation as manifested by exertional dyspnea were common. Cardiac enlargement was present in 58 of 76 patients who had roentgenograms taken prior to treatment.

The method of adjusting dosages of pentolinium tartrate has been described in previous communications.[6-8] The duration of treatment ranged from 3 to 27 months, with a mean of 12 months. Seven were treated for 24 months or longer, 44 were treated from 12 to 24 months, 26 from 6 to 12 months, and 18 from 3 to 6 months. In the majority of the cases, various other hypotensive agents were added to pentolinium tartrate for periods of time as are described below.

RESULTS

Over-all Results of Treatment

Mortality

There were 17 deaths in the entire series. Of these, 10 exhibited grade IV fundi; 4, grade III; and 3, grade II fundi prior to therapy. The survival from beginning of treatment to death in this group averaged 11 months, and in the malignant group, 13 months. The causes of death were as follows: nephrosclerosis with uremia in 11, cerebral hemorrhage in 4, rup-

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Pentolinium tartrate (Ansolysen) was generously supplied by Daniel L. Shaw, Jr., M.D., Wyeth Laboratories, Philadelphia, Pa.

TABLE 1.—*Severity Indices of Patients Prior to Treatment with Pentolinium Tartrate*

Parameter	No. of Cases	% of Total
Male	71	74
Female	25	26
Optic fundi: grade IV	34	35
grade III	20	21
grade II	40	42
grade I	1	1
Unclassified*	1	1
Elevation of blood urea nitrogen or nonprotein nitrogen	38	40
Albuminuria: 2 to 4 +	37	39
trace to 1 +	27	28
total	64	67
15 min. excretion phenolsulfonphthalein (55 cases) under 15 per cent	35	
Electrocardiogram (83 cases) LVH pattern	66	
Increased transverse diameter of heart (76 cases)	58	

* Corneal opacities prevented examination.

ture of an aortic aneurysm in 1, and myocardial infarction in 1. Twenty-four of the grade IV patients still survive, 9 have been under treatment for periods varying from 19 to 27 months, 7 from 12 to 18 months, and 8 from 3 to 10 months.

Morbidity

Myocardial infarction occurred in only one case listed above. Two patients developed persistent angina with electrocardiographic evidence of myocardial ischemia. In these two and in one other patient with electrocardiographic changes, it was necessary to discontinue pentolinium tartrate because of angina. In one other patient the routine "check-up" electrocardiogram revealed the development of a pattern consistent with an old myocardial infarction although the patient had experienced no symptoms.

In addition to the four who died with cerebrovascular hemorrages, two patients developed cerebrovascular accidents of slight degree while under treatment. Only one patient required hospitalization.

Effect on Symptoms

The results (table 2) indicate that the symptoms of headache, dizziness, palpitation and dyspnea usually improved, whereas in the case of angina a few improved but an equal number were made worse. Nocturia usually decreased but in some it increased, particularly in those who exhibited considerable postural hypotension, the latter tending to produce oliguria during the day.

Seven patients had cerebral vascular accidents with residuals prior to treatment. None showed any striking improvement, and there

TABLE 2.—*Changes in Symptoms Following Treatment*

Symptom	No. of Patients	Complete Relief	Improved	Unimproved or Worse	% Improved
Headache	53	14	30	9	83
Exertional dyspnea	25	2	17	6	76
Dyspnea at rest	15	7	6	2	87
Paroxysmal nocturnal dyspnea	5	2	3	0	100
Palpitation	6	2	2	2	67
Angina	5	0	2	3	40
Nocturia	70	21	28	11	70
Dizziness	15	5	10	0	100
CVA residuals	7			7	0

TABLE 3.—*Changes in the Optic Fundi Following Treatment with Pentolinium in Ninety-Five Cases*

Grade	No. of Patients	No. of Patients in Each Grade After Treatment				% Improved
		IV	III	II	I	
IV	34	2	6	22	4	94
III	20	0	3	13	4	85
II	40	0	0	22	18	45
I	1	0	0	0	1	0

TABLE 4.—*Changes in Cardiac Diameter as Measured Roentgenographically and Electrocardiograms Following Treatment with Pentolinium Tartrate*

Parameter Pretreatment	No. of Cases	After Treatment No. of Cases in Each Grouping				% Improved
		Normal	Improved	Unchanged	Worse	
Cardiac diameter	76					
Enlarged	58	2	33	19	6	57
Normal	18	14			4	
Electrocardiography	75					
LVH pattern	65	4	8	56	1	12
Normal	11	10				

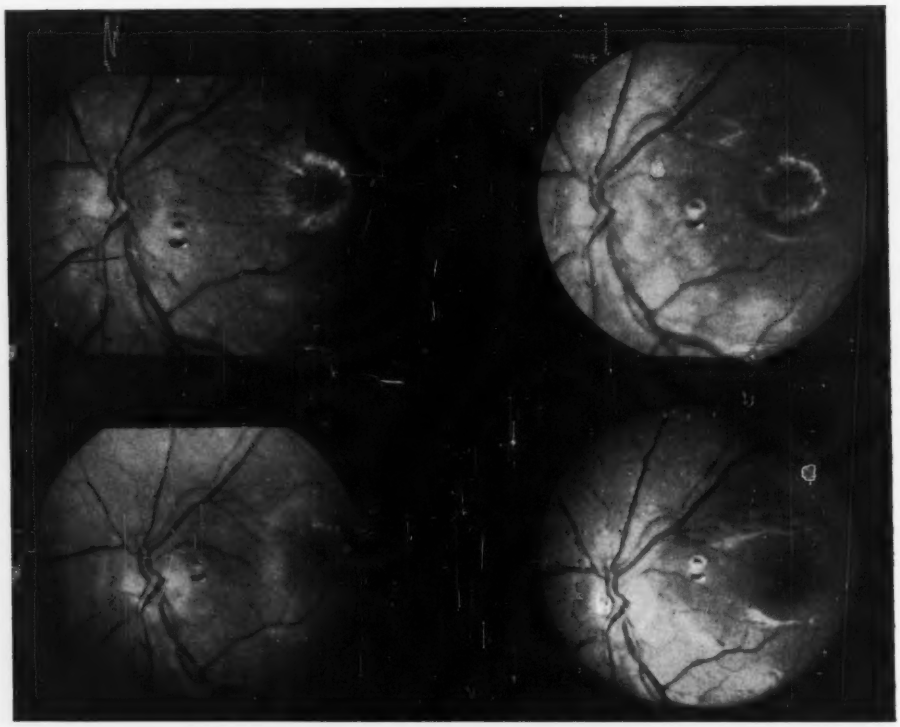

FIG. 1. Photographs of the left optic fundus in W. A., a 32 year old merchant seaman who entered the hospital with an accelerated hypertension. This could not be arrested by his family physician who had tried reserpine and hydralazine. The patient was treated with pentolinium tartrate and after 3 months returned to work as a carpenter. The upper left photograph taken prior to treatment reveals typical neuroretinitis with papilledema, a large macular "star" and a hemorrhage above the disk. The upper right photograph taken 1 month after treatment with pentolinium shows resorption of the hemorrhage and diminution in the papilledema and exudates. The lower left photograph was taken 3 months and that on the right 9 months after treatment. The fundus has reverted to grade II with residual scars in the macular area.

was a temporary return of paresis or difficulty in speech in four of these cases during periods of marked hypotension.

Effect on Objective Findings

1. *Optic Fundi.* As shown in table 3 in the total series, 67 patients, or 71 per cent, exhibited improvement in the optic fundi (fig. 1); 28 cases, or 29 per cent, remained unchanged.

2. *Transverse Diameter of the Cardiac Silhouette.* Roentgenograms of the chest were taken before and after treatment in 76 of the patients (table 4). Fifty-eight were believed to show cardiac enlargement. Thirty-three exhibited a decrease in cardiac diameter, averaging 1.3 cm. (range 0.5 to 4.5 cm.), 19 were unchanged and 6 showed an increase averaging 1.0 cm. The cardiac diameter was considered normal prior to treatment in 18 patients. Fourteen of these exhibited no significant change, while in four there was an increase in size, averaging 1.2 cm.

3. *Electrocardiographic Changes.* The electrocardiogram was recorded in 75 patients before and after treatment (table 4). Sixty-five exhibited the pattern of left ventricular hypertrophy. After treatment, 4 reverted to normal, 4 showed improvement toward normal, 56 were unchanged and 1 exhibited further progression. Of 11 patients whose electrocardio-

TABLE 5.—*Changes in Blood Nonprotein Nitrogen Urea Nitrogen Levels, Degree of Albuminuria and ifteen-Minute Excretion of Phenolsulfonphthalein ollowing Treatment with Pentolinium Tartrate*

Parameter Pretreatment	No. of Cases	After Treatment No. of Cases in Each Grouping				% Improved
		Normal	Improved	Unchanged	Worse	
Blood nonprotein nitrogen or urea nitrogen	64					
Elevated	31	8	14	3	14	45
Normal	33	28			5	
Albuminuria	76					
4 plus	10		10			100
3 plus	13	2	7	5	1	54
2 plus	7	3	6		1	86
1 plus	8	1	5	2	1	62
trace	21	4	4	8	9	19
negative	17	12		12	5	
Excretion of phenolsulfonphthalein	45					
Less than 15%	19		7	4	8	37
15 to 25%	26		4	3	19	15

grams were normal before treatment, 10 remained normal while 1 developed changes characteristic of left ventricular hypertrophy.

4. *Renal Function.* The blood nonprotein nitrogen or urea nitrogen was estimated in 64 cases before and after treatment. The results (table 5) indicate no consistent trend, some showing improvement and an equal number increasing azotemia.

The presence of albuminuria was estimated semiquantitatively using the heat and acetic acid method on freshly voided specimens of urine in 76 patients. The results (table 5) indicate that 73 per cent of the 38 patients with 1 plus or more albuminuria showed improvement.

The percentage of phenolsulfonphthalein excreted 15 minutes after injection was determined in 45 cases before and after treatment (table 5). In 26 of the cases prior to therapy, the 15 minute excretion ranged between 15 and 25 per cent of the injected dye. After treatment there was an increased excretion averaging 7 per cent above control values in of the patients, no essential change in 3 cases, while in 19 patients there was a decreased excretion averaging 10 per cent below the pretreatment level. In the remaining 19 cases the control excretion was less than 15 per cent of dye in 15 minutes; of this number 7 showed an increase following therapy averaging 8 per cent of the injected phenolsulfonphthalein, 4 were unchanged, and 8 exhibited a further decrease averaging 5 per cent.

Treatment with Pentolinium Alone

Fifty-four patients were treated initially with pentolinium for an average period of 2 months (range 2 days to 19 months, fig. 2). The average pretreatment blood pressure was 222/137 mm. Hg (range 190/110 to 270/155). Following treatment, the average pressure in the supine position was 174/106 mm. Hg (range 145/95 to 208/135), and 161/101 mm. Hg erect (range 130/88 to 200/125). This represented a reduction of "mean" arterial

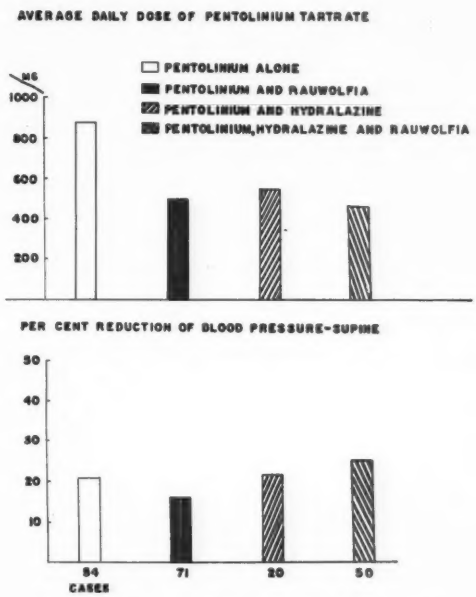

FIG. 2. Chart showing average daily dosage of pentolinium (above) and mean per cent reduction of blood pressure (below) in the group of patients treated with pentolinium tartrate alone as compared to the groups treated with the various combinations of hypotensive agents. The combination of pentolinium, hydralazine, and Rauwolfia resulted in the greatest reduction of blood pressure and the lowest dosage requirement of pentolinium tartrate.

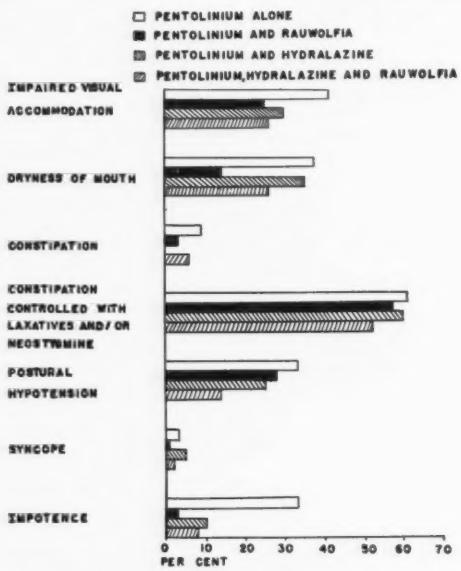

FIG. 3. Chart showing incidence of side effects of ganglionic "blockade" experienced with pentolinium tartrate alone and with the various combinations of hypotensive drugs. The incidence of such side effects appeared to be somewhat reduced with all of the combinations used.

pressure, averaging 22 per cent supine (range 11 to 39 per cent) and 26 per cent erect (range 14 to 41 per cent). The values were obtained from the average of many hospital, home and office readings; in each patient individual readings may have ranged considerably above or below the average reading.

Dosages were administered 3 times daily at approximately 8 hour intervals. The average total daily dosage was 867 mg. (range 60–1400 mg.). In many instances in order to prevent marked fluctuations of blood pressure the morning doses were smaller than the afternoon or night doses.

The incidence of side effects is shown in figure 3. Impotence was complained of in 33 per cent, although probably present in the majority of patients over the age of 45. Difficulty in emptying the urinary bladder was not complained of. Because of the development of tolerance to the hypotensive effect of pentolinium or of marked side effects from ganglionic blockade or because of marked fluctuations in blood pressure, all, except one patient, were given combinations of pentolinium with reserpine or hydralazine or both.

Pentolinium Tartrate and Rauwolfia

There were 71 cases in this group, the average duration of treatment with Rauwolfia serpentina being 6 months (range 9 days to 19 months, fig. 2). Dosages of pentolinium averaged 492 mg. (range 60 to 1800) as contrasted to 867 mg. on pentolinium alone. Rauwolfia was administered to 61 patients as reserpine in doses of 0.25 to 1 mg. per day, and as an extract of the crude root (Rauwiloid) in doses of 2 to 4 mg. daily in 10 cases.

The control blood pressures averaged 228/135 (range 200/115 to 300/170) mm. Hg. After treatment the mean supine pressure was 197/109 (range 142/92 to 250/150) mm. Hg and in the erect position 163/101 (range 130/80 to 240/145) mm. Hg. The reduction of "mean" arterial pressure averaged 16 per cent in the supine position and 26 per cent in the erect position.

The side effects of ganglionic blockade on this combination are shown in figure 3. Side effects due to the addition of Rauwolfia were nasal stuffiness in 18 per cent, severe mental depression in 6 per cent, weight gain in 21 per cent, increase in appetite in 27 per cent, nightmares in 2 patients and diarrhea in 2 cases.

In 43 patients it was possible to determine the dosage requirement of pentolinium after, as compared to before, the addition of Rauwolfia (table 6). The average daily dosage of pentolinium when used alone was 550 mg., which produced an average blood pressure fall of 18 per cent in the supine position and 22 per cent in the erect position. After addition of Rauwolfia, the average daily requirement of pentolinium was 422 mg. and the mean reduction of blood pressure was 25 per cent in the supine and 29 per cent in the erect position.

The above data represent over-all averages. In not all of the patients was it possible to reduce the dosage. In 23 or 54 per cent of the 43 patients, the dosage of pentolinium could be decreased, in 16 it remained the same and in 4 it was increased. Twenty-four patients exhibited an additional reduction of 5 per cent

TABLE 6.—*The Effect of Added Rauwolfia or Hydralazine or Both on Blood Pressure and Dosage Requirement of Pentolinium Tartrate in the Patients with Three or More Recordings of Blood Pressure Daily for Several Weeks Preceding and Following Combined Drug Therapy*

Drug Combination	No. of Cases	Pentolinium Alone			Pentolinium Combined						Cases in Which Pentolinium Was Reduced %
		Av. Daily Dose mg.	Blood Pressure Av. % Reduction		Average Daily Dose		Blood Pressure				
							Av. % Reduction		Additional % Reduction		
			Supine	Erect	Mg.	Per cent reduction	Supine	Erect	Supine	Erect	
Pentolinium tartrate and Rauwolfia	43	550	18	22	422	23	25	29	7	7	54
Pentolinium tartrate and hydralazine	13	671	18	24	610	9	24	28	6	4	54
Pentolinium tartrate, Rauwolfia and hydralazine	27	642	19	23	418	35	27	31	8	8	70

or more of "mean" arterial pressure after addition of reserpine.

Pentolinium Tartrate and Hydralazine

Twenty patients were given this combination (fig. 2). The average duration of treatment with hydralazine and pentolinium tartrate was 4 months (range 3 days to 8 months). The average daily dose of pentolinium tartrate was 671 mg. before hydralazine was added and 540 mg. afterwards. The average dose of hydralazine was 120 mg. (range 50 to 300 mg.) per day. The dosages of hydralazine were deliberately maintained at a low level because of the reported serious reactions that may occur on long term use.

The pretreatment control blood pressure averaged 227/135 mm. Hg. (range 210/120 to 250/160) in this group of cases. After treatment the average blood pressure was 173/104 mm. Hg (range 153/96 to 200/120) in the supine position. In the erect position the average blood pressure after treatment was 162/100 mm. Hg (range 140/80 to 190/110). The reduction of "mean" arterial pressure averaged 23 per cent in the supine position and 26 per cent erect.

The side effects due to pentolinium tartrate are shown in figure 3. Side effects thought to be due to the addition of hydralazine were: headache in 4, palpitation in 2 and edema in . There was no arthritis or dermatitis.

In 13 patients it was possible to compare dosage requirements and blood pressure response before and after addition of hydralazine. The results are shown in table 6. In seven patients it was possible to reduce the dosage of pentolinium.

Pentolinium Tartrate plus Rauwolfia and Hydralazine

There were 50 patients in this group (fig. 2). The average length of treatment was 4 months (range 9 days to 23 months). The average dose of pentolinium was 458 mg. (range 90 to 1700 mg.). The average dose of hydralazine was 144 mg. (range 50 to 500 mg.). Daily dosage of reserpine varied between 0.25 and 1.0 mg. per day. The average pretreatment blood pressure was 230/136 (range 190/110 to 270/170) mm. Hg. After treatment the average blood pressure in the supine position was 171/106 (range 140/90 to 200/120) mm. Hg and in the erect position was 160/99 (range 130/88 to 200/115) mm. Hg. The reduction of "mean" arterial pressure averaged 25 per cent in the supine position and 28 per cent in the erect.

The incidence of side effects is shown in figure 3. Rauwolfia side effects were: nasal stuffiness in 20 per cent, mental depression in 4 per cent, weight gain in 20 per cent, increase in appetite in 24 per cent, nightmares in 2 per cent, gastrointestinal bleeding in 2 and diarrhea in 4 per cent. Hydralazine side effects were headache in 16 per cent, palpitation in 10 per cent, and dyspnea in 1.

In 27 patients, hydralazine and Rauwolfia were added almost simultaneously (interval of 3 weeks or less). The results are shown in table 6. In 19 of the 27 patients the dosage of pentolinium could be reduced. In 9 of the patients the additional reduction of blood pressure averaged 10 per cent or more.

Development of "Tolerance"

The development of "tolerance" was estimated by comparing the dosage requirement and blood pressure reduction at the initiation of treatment with that required at the end of the period of this study. The initial effective daily dosage averaged 374 mg. and the most recent effective dosage 520 mg., an average increase of 36 per cent. In the early treatment period there was a 22 per cent reduction of supine and 26 per cent in erect blood pressure and at the end of study, 21 per cent supine and 28 per cent erect. It should be pointed out that in most instances Rauwolfia and hydralazine had been added. Thus, these figures do not accurately reflect the development of tolerance to pentolinium tartrate alone but rather to our treatment regimen.

Discussion

The symptoms that are related to hypertension or to associated cardiac decompensation often were relieved following treatment. Thus, the symptoms of headache, dizziness, dyspnea and palpitation were improved in more than two thirds of the individuals who suffered from these complaints. On the other hand, none of the patients with symptoms resulting from residuals of old cerebrovascular accidents showed improvement and in some, reduction of blood pressure aggravated these symptoms. Similarly, less than half of the patients with angina noted improvement and an equal number complained of increased discomfort. It would appear that "hypertensive" symptoms and those that arise from cardiac "strain" frequently will be improved, whereas those due to vascular sclerosis often do not improve and may become worse.

In regard to objective signs of improvement other than blood pressure, regression was noted in the optic fundi in more than four fifths of the patients with grade III and IV changes and in slightly less than half of the patients with grade II changes. Thus, the most marked effects were on the hemorrhages, exudates, and papilledema, although diminution in the degree of arteriolar narrowing also was seen in some of the cases.

In the patients with cardiomegaly diminution of cardiac size was observed in approximately one half of the cases. Since the majority of these cases had the usual therapy for congestive heart failure prior to being placed on pentolinium tartrate, the improvement appeared to result from the antihypertensive therapy per se. In fact, in many of these patients the need for salt restriction or diuretics was reduced or even abolished. In contrast to these evidences of improvement in cardiac status only 12 per cent of patients showed partial or complete reversal of the electrocardiographic pattern of left ventricular hypertrophy.

The extent of improvement in the kidneys was less impressive than in the fundi and the heart. In the patients with nitrogen retention, as many showed increasing uremia as showed clearing, and five patients developed elevations of blood urea nitrogen or nonprotein nitrogen from normal to abnormal while under treatment. The degree of albuminuria in general tended to lessen under therapy. On the other hand the ability of the patients to excrete phenolsulfonphthalein dye decreased more often than it improved.

It seems possible that the decrease in albuminuria and improvement in nitrogen retention seen in some of the cases might be expected in part on the basis of improvement in latent or overt cardiac decompensation. The same might be said for the decrease in nocturia that was frequently noted. The appearance or worsening of nitrogen retention in other patients while under therapy and the frequent observation of reduced ability to excrete phenolsulfonphthalein dye may be accounted for on the basis of two factors: (1) effect of ganglionic blocking agents on renal hemodynamics[9] and (2) further progress of the renal lesions despite antihypertensive therapy. The fact that the majority of the deaths in this

eries were due to renal failure tends to support this thesis. It would appear, therefore, hat treatment with pentolinium tartrate is east effective against the renal complications f severe hypertension. If nephrosclerosis results from sustained hypertension these observations provide an argument for beginning reatment earlier, before the renal arterioles ave become irreparably sclerosed.

Confirming our previous experience[10] and hose of others[11, 12] the addition of reserpine ot only produces a further reduction of blood ressure in many patients but also may permit reduction of the dosage of pentolinium nd, hence, lessen the incidence of disabling ide effects produced by ganglionic "blockade." This combination while effective and generally better tolerated by the patient must be instituted with an awareness that serious mental depression can occur in patients treated for long periods with Rauwolfia preparations.[13]

The additive hypotensive effect of hydralazine alone was studied in only a small number of patients and the dosages used were smaller than those employed by Perry and Schroeder in a similar study.[14] Nevertheless, the present results confirm their observation that the addition of hydralazine produced a further lowering of blood pressure. It is interesting that in our cases, where the dosages of hydralazine were small, the development of the syndrome resembling disseminated lupus erythematosus did not occur; whereas it was not an infrequent complication in Perry and Schroeder's series. On the basis of the various observations on small doses of hydralazine and of Rauwolfia we have concluded that therapy combining all 3 agents produces the greatest reduction of blood pressure and the smallest dosage requirement of the blocking agent. We believe, however, that each drug be added separately in order to judge its effects in the particular case.

It is interesting that all of the "toxic" reactions to pentolinium tartrate seemed to be due to the acute effects of ganglionic "blockade." Unlike hexamethonium[15, 16] no cases of chronic interstitial pneumonitis occurred in this series, nor to our knowledge have there been any reports of this complication in the literature on pentolinium tartrate.

The proof of the effectiveness of any form of treatment in hypertension is its ability to prevent morbidity and mortality. The duration of treatment in this series still is too short to draw any conclusions in regard to mortality. In regard to morbidity, however, it is important to note that the majority of the patients who had lost their jobs because of severe hypertension were able to return to some sort of gainful occupation. This was also the case in many of the patients who eventually died but who were able to work until shortly before exitus. The clearing of symptoms of cardiac decompensation or hypertensive encephalopathy produced considerable subjective improvement in these severe cases. In addition, due to the postural hypotension produced by pentolinium tartrate, the control of blood pressure was as good or better when the patient was up and active than when he was inactive.

The arrest and seeming reversal of ever worsening symptoms in these most severe cases provided a tremendous boost to the patient's morale, and as such was an important additional therapeutic dividend. In less desperate situations and particularly in the asymptomatic hypertensive, the side effects resulting from therapy blunted the patient's desire to continue with treatment. In such cases various technics were used to assure the patient's cooperation. These included (1) gradual elevation of dosage to the effective level, (2) explanation of side effects and instructions in minimizing their severity[5] and (3) the use of home blood pressure recordings.

Summary and Conclusions

A series of 96 patients with severe, fixed hypertension was treated with pentolinium tartrate alone or in combination with Rauwolfia or hydralazine, or both, for periods varying from 3 to 27 months (average 12 months) with the following results:

1. Ten of the 34 patients with grade IV changes in the optic fundi and 7 of the remaining cases have died. In addition, 1 case developed a myocardial infarction and 2 developed mild cerebrovascular accidents while under treatment.

2. Typical hypertensive symptoms such as

headache, dizziness and those relating to cardiac decompensation often were relieved; whereas those due to vascular sclerosis, such as angina or residuals of old cerebrovascular accidents, usually did not improve or were made worse.

3. Improvement in the optic fundi was observed in more than 80 per cent of the patients with grade III and grade IV changes and in slightly less than half of the patients with grade II changes.

4. Decrease in cardiac size frequently was observed. Improvement in the electrocardiographic pattern of left ventricular hypertrophy also occurred but less frequently than the former.

5. The degree of albuminuria usually tended to lessen during treatment. Approximately half of the patients with nitrogen retention showed clearing, whereas the other half developed increased retention. The ability of the patients to excrete phenolsulfonphthalein decreased more often than it increased following treatment. The reasons for these apparent discrepancies are discussed and it is concluded that treatment was more effective in arresting or reversing changes in the optic fundi and in the heart than in the kidneys.

6. Data are presented to demonstrate the additive effects of Rauwolfia or hydralazine, or both, to the regimen. Combining all three agents generally resulted in the greatest reduction of blood pressure with the least degree of symptoms resulting from ganglionic "blockade."

7. In view of the severity of the hypertension in the present series, it is concluded that this method of treatment is beneficial. It was especially effective in restoring semi-invalided or invalided hypertensive patients back to more useful and active modes of living.

Summario in Interlingua

Un serie de 96 patientes de sever hypertension fixe esseva tractate durante periodos de inter 3 e 27 menses (durantia median 12 menses) con tartrato de pentolinium sol o in combination con Rauwolfia o hydralazina o ambes. Le resultatos esseva le sequente:

1. Dece del 34 patientes con alterationes de grado IV in le fundos optic e 7 del altere patientes ha morite. In plus, un patiente disveloppava un infarcimento myocardiac e duo disveloppava leve accidentes cerebrovascular quando illes esseva sub tractamento.

2. Typic symptomas hypertensive—mal de capite, vertigine, symptomas pertinente al discompensation cardiac, etc.—esseva alleviate in multe casos. Symptomas debite a sclerosis vascular—angina, residuos ab ancian accidentes cerebrovascular, etc.—non se meliorava in general, e in certe casos illos deveniva pejo.

3. Melioration in le fundos optic esseva observate in plus que 80 pro cento del patientes con alterationes del grados III e IV e in levemente minus que 50 pro cento del cases de grado II.

4. Reduction del dimensiones cardiac esseva observate. Melioration del figuration electrocardiographic de hypertrophia sinistro-ventricular esseva etiam observate sed illo occurreva minus frequentemente que le reduction del dimensiones cardiac.

5. In general, le grado de albuminuria monstrava un tendentia a reducer se durante le tractamento. Circa un medietate del patientes con retention de nitrogeno habeva un augmento del clearing; le altere medietate disveloppava un augmentate grado de retention. Le capacitate de excerner phenolsulfonphthaleina esseva plus frequentemente reducite post le tractamento que augmentate. Nos discute le rationes pro iste apparente discrepantias e conclude que le tractamento esseva plus efficace in arrestar o reverter alterationes in le fundos optic e in le corde que in le renes.

6. Es presentate datos pro demonstrar le effectos additive de Rauwolfia o hydralazina o ambes. Le combination de omne tres agentes resultava generalmente in le plus grande reduction del pression sanguinee, con le minus grande grado de symptomas resultante ab "blocage" ganglionic.

7. Considerante le severitate del hypertension in le presente serie de patientes, nos conclude que iste methodo therapeutic es benefic. Illo esseva specialmente efficace in restaurar semi-invalidate o invalidate patientes hypertensive a plus utile e active formas de vita.

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Right Bundle-Branch Block. Hemodynamic, Vectorcardiographic and Electrocardiographic Observations

By EUGENE BRAUNWALD, M.D., EPHRAIM DONOSO, M.D., SAMUEL O. SAPIN, M.D., AND ARTHUR GRISHMAN, M.D.

The time intervals between the onset of ventricular depolarization and of right ventricular contraction were studied in 36 patients, by means of cardiac catheterization, and were correlated with their vectorcardiograms and electrocardiograms. The onset of right ventricular contraction was delayed in six subjects without heart disease but with the electrocardiographic picture of right bundle-branch block. The onset of right ventricular contraction was found to be normal in 10 of 15 patients with right ventricular hypertrophy with the electrocardiographic picture of right bundle-branch block. This indicates that this electrocardiographic configuration is not necessarily accompanied by delayed right ventricular contraction.

IN 1932, Wilson and collaborators[1] described the electrocardiographic patterns associated with bundle branch block experimentally produced in the dog. These classic studies have formed the basis for the electrocardiographic criteria employed in the diagnosis of bundle branch block in man. It was the purpose of this investigation to examine the validity of these electrocardiographic criteria for the diagnosis of right bundle branch block, and also to evaluate the usefulness of the spatial vectorcardiogram in determining the presence of right bundle branch block.

The simultaneous recording of the electrocardiogram with the right ventricular-pressure pulse makes possible the accurate measurement of the time interval between the onset of ventricular depolarization and the onset of right ventricular contraction. Right bundle branch block, or other disturbances in right ventricular conduction, produce a delay in right ventricular depolarization and should be accompanied by a corresponding delay in the onset of right ventricular contraction and therefore in prolongation of the time interval between the onset of the QRS complex and the onset of the rise in the right ventricular-pressure pulse. In this study both the scalar electrocardiogram and the spatial vectorcardiogram were correlated with this time interval in 3 groups of patients.

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MATERIAL

The 36 patients studied were all on the ward or private services of The Mount Sinai Hospital, New York. Group 1 consisted of 15 patients with clinical evidence of right ventricular hypertrophy, confirmed in each instance by the demonstration at the time of cardiac catheterization of a lesion that imposes a hemodynamic burden exclusively or predominantly on the right ventricle. These patients ranged in age from 3 to 34 years. Seven patients had pulmonic stenosis with normal aortic root, 5 had the tetralogy of Fallot, 1 had rheumatic mitral stenosis, 1 had an interatrial septal defect, and 1 had an Eisenmenger's complex. All 15 patients had electrocardiograms that satisfied the recently described criteria for right ventricular hypertrophy.[2] None had an RSR′ configuration in right precordial leads.

Group 2 consisted of 6 persons ranging in age from 16 to 28 years with no evidence of heart disease that could be elicited by clinical examination or cardiac catheterization. The electrocardiograms of these patients were characterized by an RSR′ pattern in the right precordial leads with a QRS duration ranging from 0.10 to 0.13 second.

Group 3 consisted of 15 patients with clinical evidence of unilateral right ventricular hypertrophy, confirmed in each instance by the demonstration, at the time of cardiac catheterization, of a lesion that imposes a hemodynamic burden on the right ventricle alone. All had the so-called right bundle-

branch-block pattern in the electrocardiogram. The 10 patients in group 3A ranged in age from 4 to 50 years. Four patients had pulmonic stenosis with normal aortic root, 4 had interatrial septal defects, 1 had a truncus arteriosus (confirmed at postmortem examination), while 1 patient had the tetralogy of Fallot. These patients all had an RSR′ configuration in right precordial leads with a QRS duration ranging from 0.08 to 0.12 second.

Group 3B consisted of 5 patients ranging in age from 16 to 64 years. Four of these patients had interatrial septal defects, while 1 had marked pulmonary hypertension during life and idiopathic nonspecific myocarditis with right ventricular hypertrophy at postmortem examination. These 5 patients also had an RSR′ pattern in right precordial leads, with a QRS duration ranging from 0.10 to 0.14 second.

Methods

Strain-gage pressure transducers (Statham P23A) were employed in conjunction with a single gun, multichannel oscilloscopic photographic recorder, in which errors of parallax are eliminated. Standard lead II of the electrocardiogram was recorded simultaneously with the right ventricular-pressure pulse in all instances. The paper speed of the recorder was 50 mm. per sec. Measurements of the time interval between the onset of QRS in lead II and the onset of the rise in the right ventricular-pressure curve were averaged for 2 respiratory cycles. The delay in the transmission of a pressure pulse through the catheter-strain-gage system has been measured and found to be close to 0.005 sec.[3] This value was subtracted from all measured intervals between electrical and mechanical events. Only records were utilized in this study in which both the onset of the QRS and of the pressure rise in the right ventricular-pressure pulse were clear.

Spatial vectorcardiograms were obtained by means of the cube method of electrode placement[4] and were photographed from the screen of a Technicon or Sanborn oscilloscope. Electrocardiograms were recorded on a 3-channel, direct-writing Technicon recorder at a paper speed of 50 mm. per second.

Results

Group 1

In this group of 15 patients with right ventricular hypertrophy, the electrocardiograms presented the pattern of right ventricular hypertrophy. The spatial vectorcardiograms showed the configuration of right ventricular hypertrophy without conduction disturbance, which has recently been described in detail.[5] The QRS loop was situated anterior to the isoelectric point and was inscribed in a clockwise direction in the horizontal plane. No abnormal slowing was noted in the inscription of the terminal portion of the QRS loop. The intervals between the onset of ventricular depolarization and of right ventricular contraction in these patients ranged from 0.045 to 0.075 second (table 1). These time intervals are within the range recently found in normal subjects.[6] Thus, in this first group of patients with clinical, electrocardiographic and vectorcardiographic evidence of right ventricular hypertrophy, the onset of right ventricular contraction was not delayed, and significant right ventricular conduction disturbance therefore did not exist.

Table 1.—*Correlation of the Electrocardiogram and Vectorcardiogram with the Time Intervals between the Onset of Ventricular Depolarization and of Right Ventricular Contraction*

Group	No. of Pts.	ECG	Range of QRS duration (sec.)	VCG	Q-RV_s (range sec.)
1	15	RVH	0.06–0.09	RVH	0.045–0.075
2	6	RSR′	0.10–0.12	RVCD	0.100–0.120
3A	10	RSR′	0.08–0.12	RVH	0.050–0.075
3B	5	RSR′	0.10–0.14	RVH + RVCD	0.095–0.120

RVH = Right ventricular hypertrophy.
RSR′ = Electrocardiographic configuration of RSR′ in right precordial leads.
RVCD = Vectorcardiographic configuration of right ventricular-conduction disturbance.
Q-RV_s = Time interval (sec.) between onset of QRS and of right ventricular-pressure rise.

Group 2

These six subjects without evidence of heart disease had electrocardiograms presenting an RSR′ pattern in right precordial leads with a QRS duration ranging from 0.10 to 0.13 second (fig. 1*A*). Spatial vectorcardiograms were obtained in three of these patients; all three had a similar configuration that indicated a conduction delay (fig. 1*B*). The major portion of the QRS loop resembled that seen in normal persons.[7] However, a distinct terminal appendage to the QRS loop was present. This

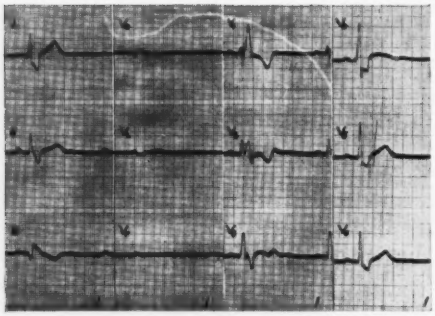

FIG. 1A. Electrocardiogram of a 16 year old boy without evidence of heart disease, taken at a paper speed of 50 mm. per second.

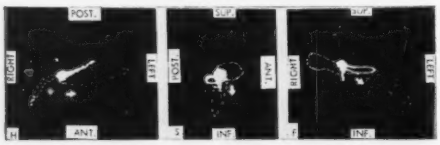

FIG. 1B. Spatial vectorcardiogram of the subject whose electrocardiogram is illustrated in figure 1A. The first portion of the QRS loop is directed to the left, inscribed in a counterclockwise direction in the horizontal plane, and resembles that seen in normal subjects. The terminal portion of the QRS loop is inscribed slowly, and is directed to the right, superiorly, and anteriorly. H, horizontal plane; S, sagittal plane; F, frontal plane.

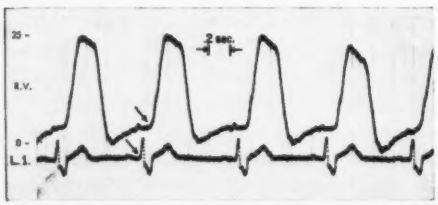

FIG. 1C. Right ventricular-pressure pulse and lead I of the subject whose electrocardiogram and vectorcardiogram are illustrated in figures 1A and 1B. The arrows indicate the onset of QRS and of right ventricular contraction, which are separated by an abnormally long interval.

appendage was directed anteriorly and to the right of the isoelectric point and was inscribed very slowly[8] (fig. 1*B*). In all six patients in this group the onset of right ventricular contraction was abnormally delayed, as evidenced by a prolongation of the time interval between the onset of QRS and the onset of right ventricular contraction to 0.10 second or longer (fig. 1*C*). These time intervals exceed those observed in normal persons.[6] In these patients the electrocardiograms and vectorcardiograms both suggested the presence of right bundle branch block, and this was confirmed by the demonstration of an abnormal delay in the onset of right ventricular contraction.

Group 3A

In this group of 10 patients with clinical and cardiac catheterization evidence of unilateral right ventricular hypertrophy the electrocardiograms showed so-called incomplete right bundle branch block, namely, an RSR′ configuration in right precordial leads with a QRS duration ranging from 0.08 to 0.12 sec. The vectorcardiograms, however, gave no evidence of conduction disturbance, and presented a configuration essentially similar to that noted in group 1, i.e., evidence of right ventricular hypertrophy. The time intervals between the onset of ventricular depolarization and of right ventricular contraction were within normal limits[6] (table 1), further suggesting that significant right ventricular conduction disturbance did not exist, despite the electrocardiographic configuration.

Group 3B

These five patients with clinical and cardiac-catheterization evidence of unilateral right ventricular hypertrophy also had electro-

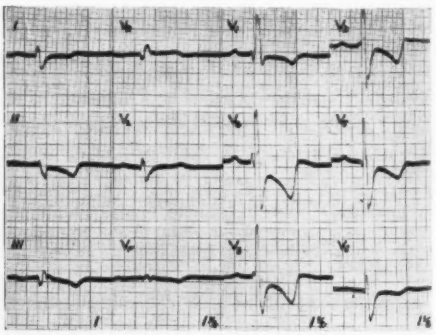

FIG. 2A. Electrocardiogram of a 36 year old man with an interatrial septal defect taken at a paper speed of 50 mm. per sec. Leads I, II, and III were taken at normal standardization, while the other leads were taken with 1 mv. = 1.5 cm.

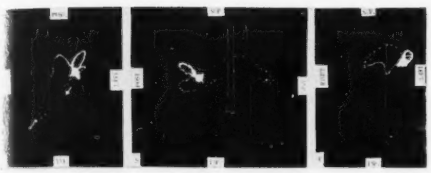

FIG. 2*B*. Spatial vectorcardiogram of the patient whose electrocardiogram is illustrated in figure 2A. The QRS loop is oriented anteriorly and to the right and is inscribed in a clockwise direction in the horizontal plane as in other patients with right ventricular hypertrophy. However, in addition, there is distinct slowing in the inscription of the terminal portion of the QRS loop, as indicated by the closeness of the dots in all 3 planes, indicating the presence of a conduction disturbance.

cardiograms with an RSR′ configuration in right precordial leads, the QRS duration ranging from 0.10 to 0.14 second (fig. 2*A*). The vectorcardiograms showed right ventricular hypertrophy, and, in addition, presented evidence of conduction disturbance. The terminal portion of the QRS loop was situated anteriorly and to the right of the isoelectric point and its inscription was distinctly slowed (fig. 2*B*). The time interval between the onset of the QRS complex and of right ventricular contraction was abnormally prolonged (table 1) to 0.095 to 0.120 sec., confirming the presence of right ventricular-conduction disturbance.

COMMENT

Previous investigations have attempted to prove the presence of bundle-branch block in man by demonstrating a prolonged time interval between the onset of ventricular depolarization and the onset of ventricular ejection. With the exception of the observations in Cournand's laboratory[9] these investigations have utilized indirect technics, such as the electrokymogram,[10, 11] the roentgenkymogram,[12] and the carotid,[10, 12, 13] or subclavian pulse[14, 15] to indicate the onset of ventricular ejection. These studies have provided conflicting results, and the accuracy of some of the indirect methods has been questioned.[16, 18] Furthermore, these technics have yielded only the time interval between ventricular depolarization and ejection, and therefore include the variable period of isometric contraction.

Using the cardiac-catheter technic the time interval between electrical and mechanical events in the human heart can be established with greater accuracy than was possible in the studies employing indirect technics. The interval between the onset of the QRS complex and the onset of the rise in right ventricular pressure is very closely related to the true time interval separating electrical and mechanical events in the right ventricle. It should be pointed out, however, that both ventricular depolarization and ventricular contraction undoubtedly commence slightly earlier than the electrocardiographic and right ventricular-pressure records indicate. Both the electrical and the mechanical processes must already be active and involve a significant portion of the myocardium before sufficient electrical potential and mechanical pressure, respectively, have been generated to produce visible deflections of the recordings. Experimental studies,[19] however, indicate that the interval between the onset of the earliest fractionate contraction in the ventricles and the onset of rise in intraventricular pressure is short indeed.

Since only right ventricular pressures were recorded in this study, the presence of abnormally asynchronous ventricular contraction could not be demonstrated. However, the time interval between the onset of ventricular depolarization and of right ventricular contraction determined in our patients could be compared with the same interval obtained in a group of normal subjects.[6] When this interval definitely exceeded that noted in the normal subjects, right bundle-branch block or significant right ventricular-conduction disturbance existed. On the other hand, a significant right ventricular-conduction disturbance could be excluded when this time interval fell within the normal range.

Right ventricular-conduction disturbances, as manifested by an abnormal delay in the onset of right ventricular contraction, were always found to be accompanied by the electrocardiographic pattern that has been designated[1] as "right bundle branch block." However, the reverse was not always found to be the case. Ten out of 15 patients with right ventricular hypertrophy and the electrocardiographic

pattern of right bundle branch block failed to show delayed onset of right ventricular contraction. The spatial vectorcardiogram appears more reliable than the scalar electrocardiogram in detecting the presence of right ventricular-conduction disturbance. An anteriorly directed, abnormally, slowly inscribed, terminal phase of the QRS loop was observed in all patients with delayed onset of right ventricular contraction, but this vectorcardiographic pattern was absent in all patients with a normal onset of right ventricular contraction. The vectorcardiogram appears to be of particular value in patients whose electrocardiograms show an RSR′ pattern in right precordial leads. It effectively separates these patients into 3 distinct categories: (1) those with right ventricular-conduction disturbance without right ventricular hypertrophy, (2) those with right ventricular hypertrophy without right ventricular-conduction disturbance, and (3) those with right ventricular-conduction disturbance in the presence of right ventricular hypertrophy.

It has recently been noted[20-22] that following cardiac surgery on patients with pulmonic stenosis and interatrial septal defect the electrocardiographic picture of so-called "incomplete right bundle branch block" has emerged from that of right ventricular hypertrophy. These observations further suggest that in patients with congenital heart disease and anatomic right ventricular hypertrophy, the electrocardiographic configuration of "right bundle branch block" does not always represent a conduction disturbance, but may reflect the presence of right ventricular hypertrophy. In the present study, no significant conduction disturbance could be demonstrated by the measurement of the time intervals between electrical and mechanical cardiac events in 10 of 15 patients with congenital heart disease, right ventricular hypertrophy, and the electrocardiographic pattern of right bundle branch block.

Summary

1. The time intervals between the onset of ventricular depolarization and of right ventricular contraction were obtained by cardiac catheterization in 36 patients, and were correlated with the spatial vectorcardiogram and the electrocardiogram.

2. In 15 patients with clinical, electrocardiographic and vectorcardiographic evidence of right ventricular hypertrophy, the onset of right ventricular contraction followed the onset of the QRS complex by normal intervals (0.045–0.075 sec.), indicating that significant right ventricular conduction disturbance did not exist.

3. In six subjects without heart disease whose electrocardiograms and vectorcardiograms showed right bundle branch block, the electric-mechanical intervals were prolonged (0.095–0.110 sec.), confirming the presence of conduction disturbance.

4. In 15 patients with clinical evidence of right ventricular hypertrophy the electrocardiograms showed right bundle-branch block. In 10 of these the vectorcardiograms showed right ventricular hypertrophy without conduction disturbance, and this interpretation was confirmed by a normal electrical-mechanical interval. Thus, right ventricular contraction was not delayed in spite of the electrocardiographic configuration of right bundle branch block. In five such patients, however, the vectorcardiograms gave evidence of right ventricular hypertrophy and conduction disturbance, and the onset of right ventricular contraction followed the onset of the QRS complex by abnormally long intervals.

5. The spatial vectorcardiogram is useful in detecting the presence of right ventricular conduction disturbance.

Acknowledgment

The cardiac catheterizations were performed in conjunction with the other members of the cardiac catheterization team under the direction of Dr. Alvin J. Gordon.

Summario in Interlingua

1. Le intervallos de tempore inter le declaration del dispolarisation ventricular e le contraction dextero-ventricular esseva obtenite per catheterisation cardiac in 36 patientes. Illos esseva correlationate con le vectocardiogramma spatial e le electrocardiogramma.

2. In 15 patientes con clinic, electrocardiographic, e vectocardiographic evidentia de hypertrophia dextero-ventricular, le declaration del contraction dextero-ventricular sequeva le declaration del complexo QRS per intervallos normal (0,045 a 0,075 secundas). Isto indicava que un significative disturbation del conduction dextero-ventricular non esseva presente.

3. In 6 subjectos sin morbo cardiac sed con electrocardiogrammas e vectocardiogrammas indicative de bloco de branca dextere, le intervallos electrico-mechanic esseva prolongate (0,095 a 0,110 secundas) e confirmava assi le presentia de un disturbation del conduction.

4. In 15 patientes con evidentia clinic de hypertrophia dextero-ventricular, le electrocardiogrammas indicava bloco de branca dextere. In 10 de iste casos le vectocardiogrammas indicava hypertrophia dextero-ventricular sin disturbation del conduction, e iste interpretation esseva confirmate per un normal intervallo electrico-mechanic. Assi, le contraction dextero-ventricular non esseva retardate in despecto del configuration electrocardiographic indicative de bloco de branca dextere. In 5 tal patientes, del altere latere, le vectocardiogrammas indicava hypertrophia dextero-ventricular e disturbation del conduction, e le declaration del contraction dextero-ventricular sequeva le declaration del complexo QRS per anormalmente longe intervallos.

5. Le vectocardiogramma es utile in le detection del presentia de un disturbation de conduction dextero-ventricular.

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Observations on Vascular Sounds: The "Pistol-Shot" Sound and the Korotkoff Sound

By RAMON L. LANGE, M.D., ROBERT P. CARLISLE AND HANS H. HECHT, M.D.

The similarity between spontaneous "pistol-shot" sounds heard over large vessels and the Korotkoff sounds heard distal to a partially inflated blood pressure cuff suggests that a similar mechanism is responsible for their occurrence. Simultaneous records of intravascular pressures and of the sounds demonstrate that the sounds generally precede the major rise in intravascular pressure. These observations cannot be explained by the existing theories of sound production. A possible mechanism based on rapid changes in flow pattern is advanced.

DESPITE continued interest in the nature of sounds that occur along the course of an artery distal to a segment compressed by an inflated cuff at a pressure between systolic and diastolic (Korotkoff sounds),[1-8] little consideration has been given to the spontaneously occurring "pistol-shot" sounds heard under certain circumstances over the larger arteries. That these spontaneous vascular sounds may be related to the sounds elicited by the cuff is suggested by the occasional indirect blood pressure recording of "zero diastolic pressure," which implies that sounds continue to be heard distal to the cuff even when the cuff has been completely deflated. This suggests an imperceptible transition between cuff-induced and spontaneous vascular sounds. Adequate correlation between these sounds, vascular pressures, and flow depends on simultaneous recordings of these events. The following method was employed in order to elucidate the interrelationship of these events.

METHOD

Intra-arterial pressures, both femoral and brachial, were measured by inserting a No. 20 or No. 18 needle into the vessel through the intact skin. The needle was connected to a capacitance electromanometer by a polyethylene tube of 80 cm. length and 3 mm. inside diameter. The output of the electromanometer was fed to 1 beam of a twin beam oscilloscope. The second beam recorded the vascular sounds by means of a bell-type carbon microphone amplified through a Heathkit WAP-2 preamplifier. The two beams were adjusted to deflect through the same "Y" axis and were photographed by a camera with a film speed of 250 mm. per sec. The time constant of the pressure system was 4 sec. At times, a strain-gage mirror galvanometer system was used and records obtained by means of a kymographic camera. The natural frequency of the latter was at 50 cps, whereas the response of the former was flat to over 500 cps. The slight elastance of the tubing caused a lag of 4 msec. of pressure behind sound. (One mm. at 250 mm. per sec. camera speed.) On several occasions, cardiac output was determined by venous catherization or by the pressure pulse method. For the latter, a Peterson-type arterial catheter was inserted into the root of the aorta through a No. 18 needle placed in the femoral artery, and the stroke volume was determined by the method of Warner and co-workers.[17] In experiments of this sort, the slope of the rising portion of both the central and the peripheral pulse in mm. Hg per sec. was also measured. Observations were obtained on 8 normal subjects, on 6 patients with aortic incompetence, and on 1 patient with untreated thyrotoxicosis. The normal subjects were studied at rest and after breathing 10 per cent oxygen or following the intravenous administration of two vasodilators, Apresoline or Priscoline, in order to study the effects of increased systemic flow with or without significant vasodilatation. All subjects were studied in the supine position, and measurements were made at rest or in what was assumed to be a "steady state." Sounds were recorded above, below, and at the level of the needle tip in the artery. When Korotkoff

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TABLE 1.—*Relations of Flow, Rate, Duration and Degree of Pressure Rise, Blood Pressure, and Vascular Sound*

Subject	Cardiac Output l/min	Stroke Volume ml./beat	Arterial Pressure mm. Hg		Vascular Sounds	Anacrotic Slope of Arterial Pulse mm./Hg/sec.		$\Delta P/t$	Remarks
			Cuff	Direct		Central	Peripheral		
J. M. Normal	7.2	120	130/70	130/70	−		960	60/0.07	
	9.0	121	125/65	125/65	++*		1200	60/0.05	10% O_2 inhalation
	18.7	170		130/70	++++		1400	60/0.04	10% O_2, 50 mg. Priscoline, i.v.
W. J. Normal	7.7	101		140/80	−		1000	60/0.06	
	9.4	94		150/60	+*		1200	90/0.08	10% O_2 inhalation
	14.7	136		175/75	+++		1500	100/0.07	10% O_2 inhalation, 50 mg. Priscoline, i.v.
E. L. Normal			120/80	120/80	−	450	500	40/0.08	
W. H. AI			170/0	160/50	++++	970	1200	90/0.08	
V. G. AI			170/0	165/55	++++	700	820	110/0.13	
L. S. RHD	2.8	45	00/00	150/80	−	500	1000	50/0.05	Severe failure ("shock")

* = Over femoral vessels only.
AI = Aortic insufficiency, no failure.
RHD = Rheumatic heart disease.
$\Delta P/t$ = Absolute rise in pressure (mm. Hg) per duration of pressure rise.

sounds were investigated, both sound and pressure were recorded 1 cm. below the distal cuff edge. Representative data showing relations between sounds and flow rates, and characteristics of the pulse wave in the various states studied are shown in table 1.

EXPERIMENTAL OBSERVATIONS

As is seen in figure 1, sounds heard over locations extending from the abdominal aorta to the dorsalis pedis artery are characterized by brief, rather intense vibrations with durations of 16 to 50 msec. and frequencies of 100 to 200 cps. Figure 2 shows pressure and sound recorded at the needle tip (I), 25 cm. above and below the tip, (II and III), demonstrating that the sound precedes the pressure rise by 10 to 12 msec. From II and III, it is obvious that the sound is propagated along the artery at a velocity of approximately 8 M. per sec. This is in close agreement with known values for pulse wave propagation.[14] In IV and V, the needle was rotated 180 degrees around its long axis resulting in the appearance of a definite negative preanacrotic dip of 8 to 10 mm. Hg. This was readily reproducible and may be the same phenomenon that Erlanger recorded as a vessel wall movement.[4] (To avoid deforming the vessel wall, in IV and V, the microphone bell was placed 25 cm. above the needle.)

Figure 3 shows the relationships of sound and lateral movement of the vessel wall using a pressure capsule. Sound was recorded as indicated in the legend. Again from the average values for I and IV the sound is recorded 10 to 12 msec. before the first lateral movement of the vessel wall. This same sequential relation of spontaneous sounds to pressure has been found in all patients with aortic valve incompetence, in a normal 22 year old woman in her first trimester of pregnancy, in a 28 year old man in a thyrotoxic state, and also in subjects in whom the stroke volume and cardiac output were increased by the inhalation of 10 per cent oxygen or by the intravenous administration of Priscoline or Apresoline.

The sequence of events in the brachial artery immediately below a standard blood pressure cuff which is inflated to above systolic pressure and slowly deflated to below diastolic pressure is shown in figure 4*A*. Line I shows that the sounds appear ahead of the main pulse rise by a time period comparable to that seen in spontaneous sounds. Note, however, that there is a slight rise in pressure (indicating small flow) at the time of sound production, which 16 to 18 msec. later changes to the usual rapidly rising pulse contour. The relative flow rates cannot, of course, be quantitated. The

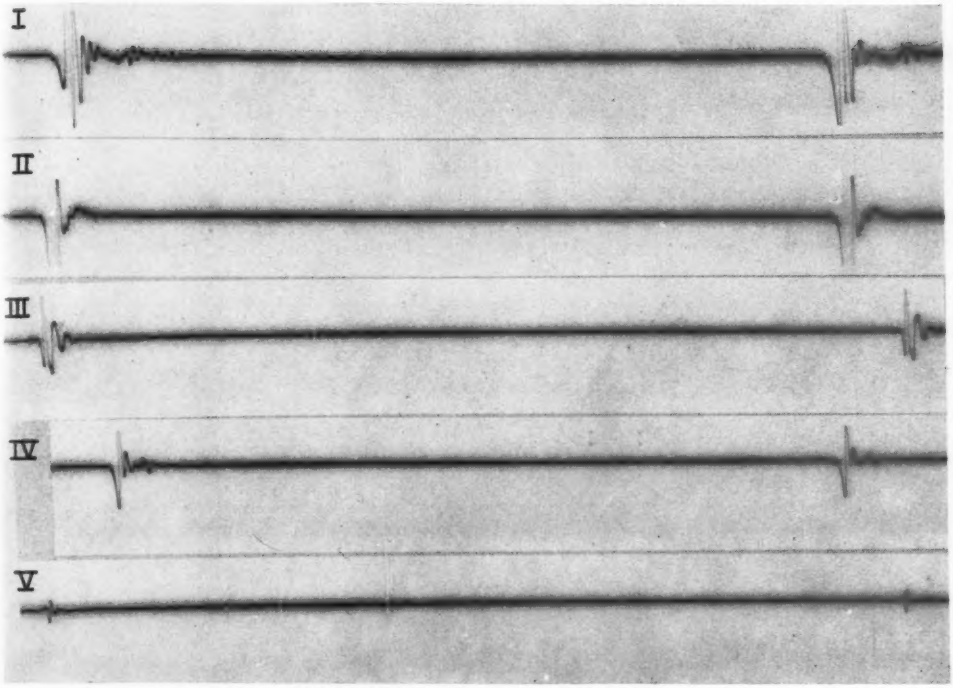


FIG. 1. Lines I to V show appearance of spontaneous "pistol-shots" as recorded at umbilical (I), femoral (II), mid thigh (III), popliteal (IV), and over the dorsalis pedis (V) level respectively. Subject W.H.

sound is again of short duration, of relatively high intensity, and has a frequency of 100 to 150 cps. Figure 4*B* shows that the Korotkoff sounds, line I, differ from the spontaneous sounds, line III, only in frequency and in intensity. Line I shows duplication of the first recorded sound at cuff pressure just below systolic. Line III shows the decrease in frequency as the cuff pressure is decreased from 50 to 20 and to zero mm. Hg.

Theoretic Considerations

The above observations demonstrate that there exists a close resemblance between spontaneous and induced sounds in blood vessels. The additional fact that at times it is clinically impossible to distinguish between them suggests a common or closely related mechanism. The records show that (1) at a given point in the arterial tree, the "pistol-shot" precedes both the pressure rise and the lateral movement of the vessel wall. In the case of the induced sounds, (Korotkoff), the sound also precedes the main pulse wave; (2) the duration of the sounds is such that the sound disappears before the pressure rise is complete (thus discounting the possibility that the sound is transmitted down the vessel from the upstream pulse wave); (3) the duration of the spontaneous sound is nearly equal to the time of rapid pressure rise and also rapid caliber change of the vessel from which the sound arises.

A number of explanations have been proposed for vascular sounds of the type under discussion, which may be briefly listed as follows: (1) sudden expansion of the vessel wall and resultant vibration and sound production;[3, 5, 6] (2) the "water-hammer" effect due to sudden change in flow or pressure;[1, 2, 8] (3) the "preanacrotic phenomenon" or "breaker effect" relating the sound produced to surface wave phenomenon;[4, 5] (4) fluttering of the

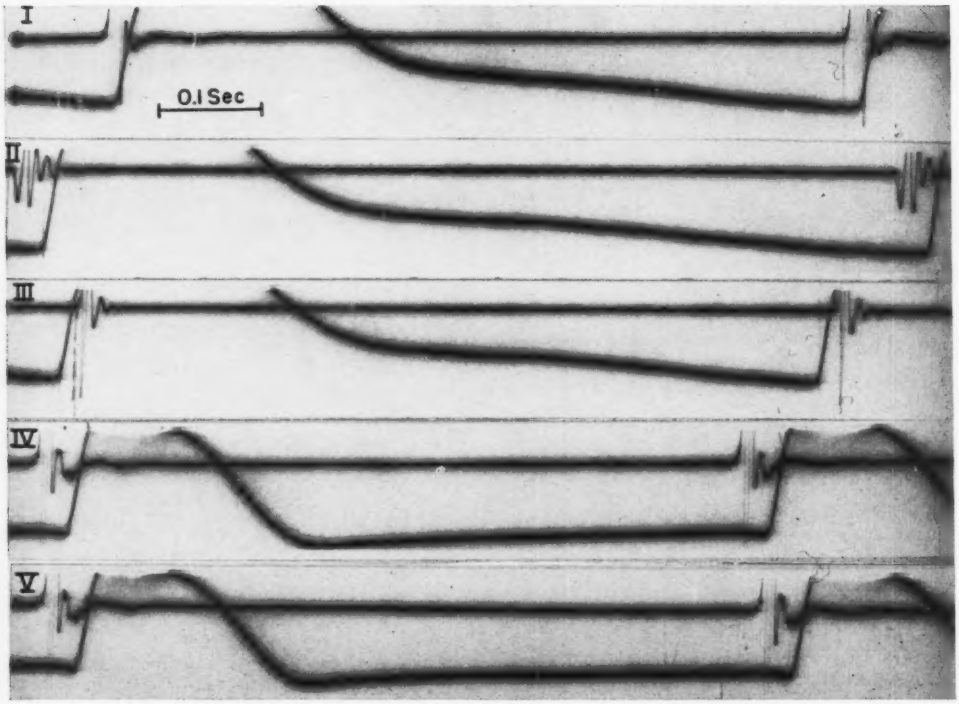


FIG. 2. Simultaneous records of pressure in femoral artery with microphone: I, over needle tip; II, 25 cm. above the needle; III, 25 cm. below the needle; IV and V, 25 cm. above the needle tip (umbilicus), but needle rotated 180 degrees around long axis. Subject W.H.

vessel wall during flow through a compressed segment, the "Bernoulli effect."[3, 7]

In the light of the above observations, these explanations for the production of vascular sounds need to be scrutinized.

1. *Sudden Expansion of the Vessel Wall Caused by the Pulse Wave.* The duration of the anacrotic pressure rise in the case of the patient in figures 1, 2, and 3 as measured by strain gage is .08 sec. (col. 8, table 1). It is unlikely that such a transient wave, which is at best 6 cps, would impart a vibration of up to 200 cps to the vessel wall, since the total duration of the induced vibration is less than one complete cycle of the inciting wave.

2. *The "Water-Hammer" Effect.* The strict definition of "water-hammer" requires that a rigid system transmit a compression wave at a velocity that approaches the speed of sound in liquid.[9, 15] The observed transmission velocity, (8 M. per sec.) is approximately 1/200 that of a true "water-hammer," and for this reason the explanation does not appear valid.

3. *The "Preanacrotic Phenomenon."* The recording of the preanacrotic phenomenon, (negative dip, fig. 2), whose presence depends upon the direction of the needle opening, indicates a disturbance in flow pattern ahead of the pulse and is only seen in fortuitous circumstances. Erlanger[4] showed the presence of this dip in arteries under pneumatic compression. He surmised that Korotkoff sounds occurred when the dip was present but no simultaneous measurements were made. As figures 2, 4*A*, and *B* indicate, spontaneous as well as induced vascular sounds occur in the absence of the "dip."

4. *The "Bernoulli Effect."* Rodbard,[7] on the basis of vibrations in a thin-walled system using a low viscosity liquid, suggests that the blood flowing through the segment of compressed vessel reaches a high velocity. The

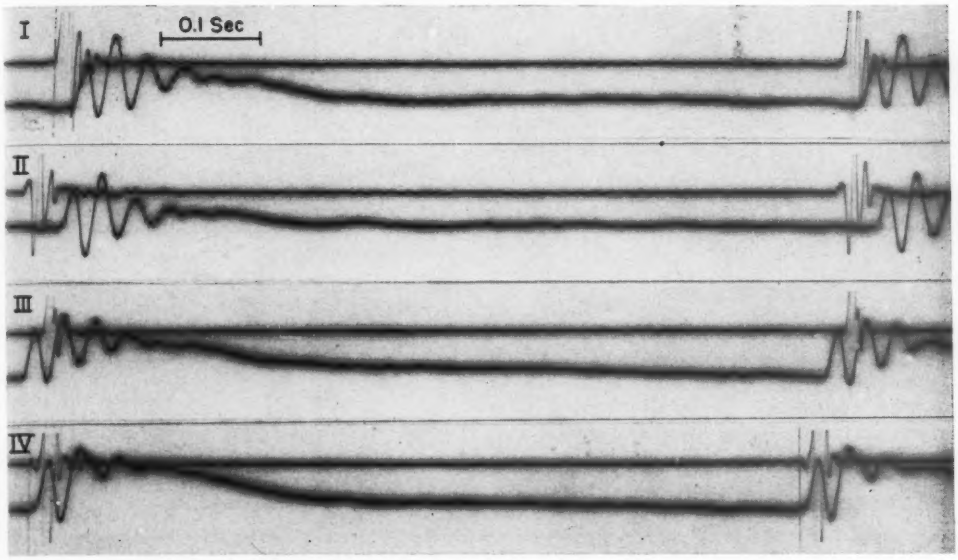


FIG. 3. Simultaneous records of sound and lateral movement of the vessel wall: I, microphone just above the capsule; II, microphone 25 cm. above the capsule; III, microphone 25 cm. below capsule; IV, microphone just below the capsule. Subject W.H.

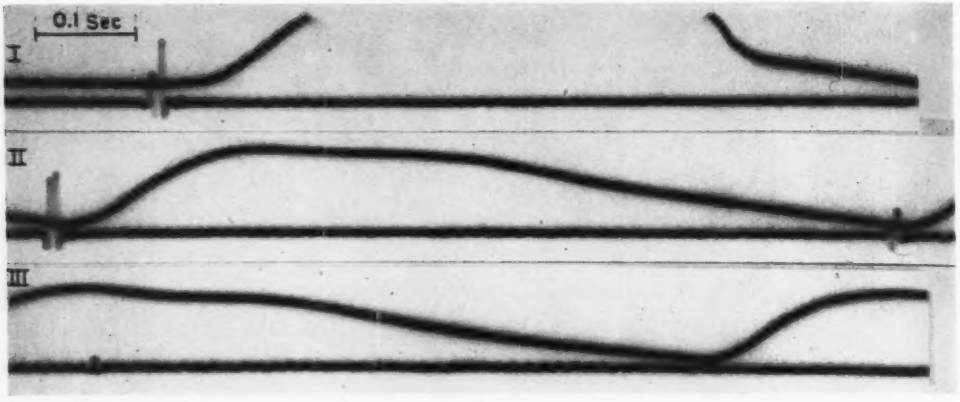
"Bernoulli effect" of a decreasing lateral pressure as velocity is increased would tend to cause an intermittent flow with resultant wall vibration. The physical differences between the thin-walled model "artery" in air through which a low viscosity liquid is passed and the brachial artery, surrounded by semi-fluid soft tissue (and then surrounded by a pneumatic elastic cuff) through which a much more viscous blood flows, casts doubt that the "Bernoulli effect" can be applied to the production of the Korotkoff sounds. The observation that these sounds are heard over a very localized area immediately below the cuff attests to the damping effect of the relatively thin layer of subcutaneous tissue that covers the brachial artery at the antecubital space. In any event, this mechanism could not explain the spontaneous sounds shown in figure 4*B*, line III, which have the same time relationship as the Korotkoff sounds, since at no time is the vessel segment empty or even compressed when spontaneous sounds are present.

Luisada and Rappaport,[3] suggest that factors (3) and (4) operate in the production of Korotkoff sounds. The discrepancies discussed above apply equally to this suggestion.

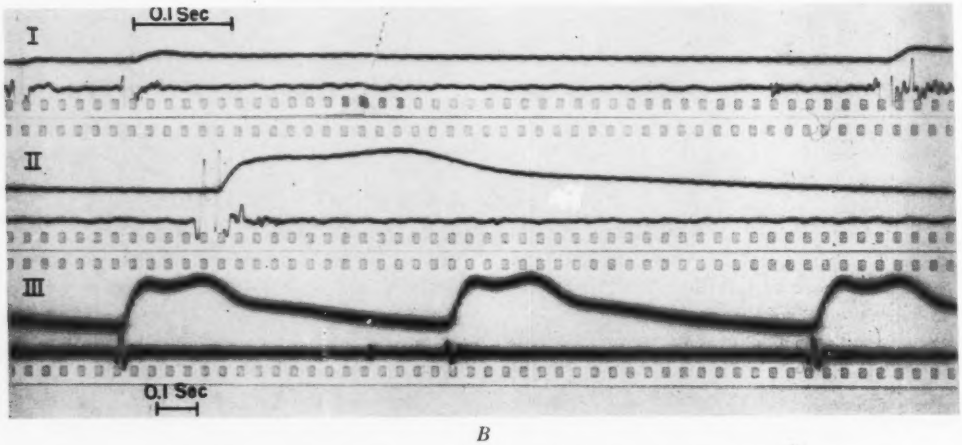
Because these explanations do not satisfy the observed facts, another mechanism for the observed sounds is proposed that is based on known concepts of fluid mechanics.[15] For orientation, the following definitions are set forth.[9, 15]

1. *Steady flow* is the flow in which the velocity, pressure, density, and so forth, at a given point do not change with time. This may be termed silent or quiet flow. The usual flow in vessels may be a gradually changing continuum of steady flow.

2. *Laminar flow* is the form of steady flow in vessels where the fluid moves in layers, one layer tending to slide with respect to its neighbor, (intermolecular friction). There is no transfer of fluid mass between adjacent layers. In Newtonian fluids, such as water, the velocity distribution across a circular vessel when seen in two dimensions (fig. 5) is a parabola with the velocity of the lamina at the wall zero, the velocity at the center twice mean velocity. Blood, however, is not a New-



A



B

FIG. 4. *A*, Simultaneous Korotkoff sounds and brachial artery pressures taken from a point 1 cm. below the cuff edge (see text). *B*, Simultaneous Korotkoff sounds and pressure as in 4 *A*, line I and II. Line III at slower film speed shows the transition from Korotkoff sounds to spontaneous sounds indicated by the change to a lower frequency. Note that the time relationship remains the same. It is interesting that the extreme "dicrotic" pulse had two peaks with duplication of Korotkoff sounds at cuff pressure near systolic levels (line I, 2 sounds with each pulse).

tonian fluid and may follow a blunted parabolic velocity profile (fig. 5).

The formula for the velocity of any lamina (v_i) at distance x from the center of a vessel radius R through which a fluid is flowing with a mean velocity of $\bar{v}$, is expressed in the following equation[9]:

$$v_i = (R^2 - x^2)(2\bar{v}) \qquad (1)$$

3. *Turbulent flow* is characterized by secondary, irregular motions and velocity fluctuations that are superimposed upon the principal, or average, flow. There is crossing of flow lines, and eddies are formed. Energy is therefore dissipated which does not contribute to the average forward flow. With the liberation of energy turbulent flow eventually reconverts to a laminar flow pattern. Turbulent flow is a form of *unsteady flow* and as such is known to be a source of noise or sound.[15]

4. Since the ratio of inertial energy to viscous force in a flowing system determines

whether laminar or turbulent flow is present, the dimensionless ratio, the *Reynolds number* has been used to predict which type of flow will occur. This may be expressed in the form of equation 2, where viscosity and density are constant.[15]

$$R_e = k\bar{v}R, \qquad \bar{v} \text{ and } R \text{ as before} \quad (2)$$

The Reynolds number (R_e) at which turbulence occurs is 2000. Thus equation 2 shows that, for a given velocity, turbulence will be more likely to occur as the radius increases. It has been calculated that flow in the aorta normally approaches turbulence.[19]

In addition to these definitions further parameters of pulsatile flow in an expansile system may be listed:

1. *Pulse wave velocity*, 4 to 8 M. per sec., a value that can be determined accurately between two points (mean pulse velocity). This is, of course, independent of any net movement of fluid. Indeed, considerable pulse wave velocity along the vessel may be present in the absence of any flow within the vessel and may be present even with blood flowing in the opposite direction (venous pulse). The speed of propagation of the pulse wave is primarily dependent on the distensibility of the vessel wall and on the density of the fluid which it contains. It can be predicted by empirical relationships.[14]

2. *Flow*, expressed as volume transported past a point per unit time, is more difficult to measure without disturbing the system. Despite conflicting results by different methods[10-12, 16, 17, 19] it is safe to say that blood passes through the aortic valve as a pulse, all the flow in systole, none in diastole. At some point along the aortic reservoir, this completely pulsatile flow is changed to more or less constant run-off at the arteriolar end of the vascular system.

3. *Linear velocity*, cm. per sec., is not constant at all points across the vessel diameter and should, therefore, be referred to as *mean linear velocity* even though it is an instantaneous value. It is independent of the speed of the pulse wave and in the dog's aorta has been estimated at from 80 cm. per sec. systolic to 8 cm. per sec. diastolic.[10, 12] Mean linear

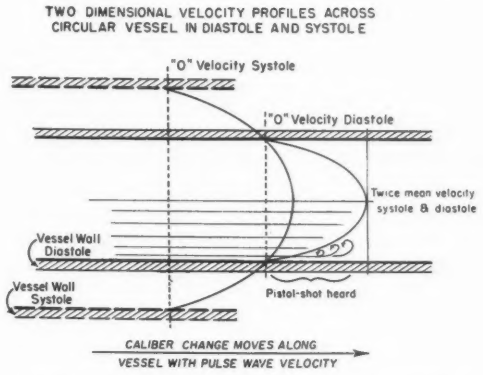


FIG. 5. Schematic representation of change in velocity profile of laminar flow patterns which occurs with increasing caliber without change in mean linear velocity.

velocity through the aortic valve is high in systole and zero in diastole. If this would continue in the aorta and larger vessels, the increase of cross sectional area caused by the expanding vessels would exaggerate the pulsatile nature of the flow. (Flow equals $\bar{v} \times A$, where A is the cross-sectional area.) This is contrary to actual observation. In calculations of stroke volume from the central pulse it may be noted that without additional inflow, two thirds of the previous systolic stroke volume leaves the arterial reservoirs during diastole.[17] Therefore, the rate of flow during diastole is only slightly smaller than that during systole. In addition, the normal central pulse shows a declining limb of the pressure tracing during diastole that deviates from a straight line only by the superimposed incisure of the aortic valve closure. From known pressure-volume relationships of the human aorta[13] this straight line slope might be interpreted as a linear decrease in the aortic and large vessel volume which can only be due the constant forward run-off. (No blood passes the aortic valve during diastole.) Assuming no significant change in the length of the system, the cross-sectional area of the vascular bed (aorta and great vessels) would decrease during diastole at the same rate as the volume decreased. Because $\bar{v} = F/A$, (Flow/Area cross-section) a linear increase in mean velocity must occur in diastole. Mean linear velocity

must then decrease during the following systole. The actual velocity changes are probably not great and occur gradually. (This does not agree with measurements made with bristle, "bubble," and differential-pressure flow meters and is merely indirect evidence for events that are very difficult to record instantaneously.) This indicates that in the great vessels at the end of diastole, the blood has not only appreciable linear velocity, but may well be at a near peak value at that time.

The recorded sequence of sound and pressure changes in vessels could be explained as two phases of relatively steady, quiet flow separated by a brief period of extremely unsteady or turbulent flow that begins just ahead of the pulse pressure rise. From the definition of laminar flow, it is apparent that, for a given mean velocity and diameter of vessel, an individual velocity distribution across the vessel diameter will be set up. Either a change in diameter, or in mean velocity, will be associated with a change to a second velocity distribution with appropriate changes in potential and kinetic energy. In an expansile system such as the arterial tree, the important change is due to change in the vascular diameter. This undergoes more rapid changes than does the mean velocity.

If this change occurs rapidly, the sharp disturbance in flow pattern will result in a transient period of turbulent flow and in the release of energy that may be manifested as sound (fig. 5). As energy is dissipated, a new laminar flow pattern becomes established. (This situation is analogous to the "hydraulic-jump" in which turbulent flow and energy loss separates two laminar flow patterns at different mean velocities and cross-sectional areas.[9]) Helps and McDonald,[16] using high-speed photography of the movement of gas bubbles in a vessel, have found oscillatory movements of high velocity and short duration at the time of pressure rise.

Going a step further (fig. 5), if the sudden change in diameter is moving along the vessel (as a propagated pulse wave would), a brief, sharp sound might be heard as the disturbance passes under the microphone or stethoscope. Since the slow moving laminae near the wall of the vessel in diastole are being acted on by an accelerating force from the faster lamina in the larger caliber portion of the vessel in systole (fig. 5), turbulent flow may occur at the end of diastole several milliseconds ahead of the arrival of the pressure pulse. It will continue several milliseconds after the arrival of the rise in pressure as energy is being "bled-off" the blood in the vanguard of the pulse. This explanation seems to satisfy the recorded sequence of events (figs. 2 and 3).

The changes in flow pattern that have been discussed may to a certain extent be quantitated. Distensibility studies of the human aorta[13] indicate that in the aorta of a young individual a pressure rise of from 40 to 160 mm. Hg (aortic insufficiency, W. H., table 1), would give approximately a threefold increase in volume. If this occurs without a change in length of the vessel, the radius should increase by 1.7. Assuming that no significant changes in mean velocity have occurred as the radius is increased and assigning a value of 50 cm. per sec. as mean velocity, the relative changes in velocity distribution occurring within this vessel can be calculated by substitution in equation 1. As the vessel radius increases by 1.7, the lamina which in diastole had zero velocity ($x = R$) must accelerate to $x = 1/1.7R$ during systole (fig. 5). Therefore, $V_i = (1 - .36)\ (100) = 64$ cm. per sec. If the time in which this change must take place is of the order of 0.1 sec this would require an average acceleration of 6.4 M. per sec.^{2} Most of the energy released by this acceleration is absorbed by the distal column of blood still in the diastolic portion of the pulse curve. Some of the energy that cannot be transferred to flow will manifest itself as noise by unsteady flow.

At the other extreme, a subject such as E. L., table 1, with arterial pressures of 120/80 mm. Hg could have a corresponding volume change of arterial reservoirs with the radius increasing by only 1.2.[13] Assigning a mean velocity of only 25 cm. per sec., the systolic velocity assumed by the lamina with zero diastolic velocity (that nearest the vessel wall) could be expressed by $V_i = (1 - .7)\ (50) = 17$ cm. per sec. If the pressure rise takes place over 0.1 sec., the acceleration of that lamina undergoing the greatest change in velocity would only be 1.66 M. per sec. In the first case, with spontaneous vascular sounds, the cross-sectional area involved in a velocity increase is twice that in the second case which showed no spontaneous sounds. Thus the increase in inertial energy in the first case would be greater and would occur over a shorter period of time than in the second case. (See Appendix.) It can, therefore, be stated that the change in energy level responsible for the source of sounds will be

nction of several somewhat interdependent factors:) the degree of pressure rise (ΔP); (2) the slope the pressure rise, dP/dt; (3) the increase in cross- ctional area for a given pressure rise, dA/dP and) mean linear velocity ($\bar{v}$) at the end of diastole. hus, the energy per unit time imparted to a col- nn of blood in diastole by an advancing pulse essure wave may be expressed in a general equa- on as:

$$E_s - E_d = Kf[\Delta P,\ dP/dt,\ Da/dP,\ (\bar{v})] \quad (3)$$

here $E_s - E_d$ is the increase of energy, both pres- ure and kinetic, by the pulse wave and K is a roportionately constant. J. M., table 1 shows hanges in the various factors of equation 3 ex- ibited by a normal individual with "quiet" vessels t rest who developed spontaneous sounds over the emoral arteries while breathing 10 per cent oxygen nd after intravenous Priscoline. Note that without hange in pressure (ΔP), the rate of pressure rise (dP/dt) in the radial artery (col. 8) increases during noxia and after Priscoline. This results in a more apid caliber change than at rest. At the same time, both stroke volume and cardiac output rise (col. 3 and 4) with corresponding increase in mean veloc- ity ($\bar{v}$). The changes will cause a several fold in- crease in energy transfer during the experimental procedures as compared to the resting values.

A second type of sound occurring spontane- ously over vessels is seen in figure 2. This is a low intensity, crescendo and decrescendo sound that occurs after the plateau of systolic pressure has been reached. The contrast be- tween this and the brief, sharp "pistol-shot" is considerable. From the definition of Rey- nold's number and equation 2, either an in- crease in radius or in mean velocity would cause turbulent flow in a system where the critical Reynold's number was approached. The fact that this low-grade turbulent flow does not persist throughout systole can be explained by the previously suggested inverse relationship between pressure and mean linear velocity in the great vessels.

A similar interpretation may be advanced or the case of sounds heard over a vessel onstricted by a cuff. Because of the elasticity f the skin, and the semifluid properties of at and muscle, the compression force of the uff is transmitted to the vessel better at the uff center and less well at the cuff edges. This schematically depicted in figure 6. As is ndicated, condition I shows the vessel just rior to penetration by the pressure pulse.

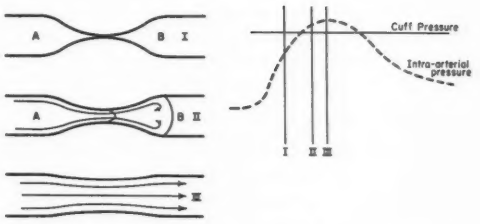


FIG. 6. Schematic suggestion of relationship between cuff pressure and the shape of and flow through a vessel over which sounds of Korotkoff are heard.

As penetration begins, condition II, there may be a small amount of flow through a deformed segment with the formation of turbulent flow distal to the deformity. Condition II is very brief in duration, since the pressure rise continues and the deformity is quickly obliterated. Thus condition II quickly changes to condition III which allows relatively steady laminar flow during the time the main pulse wave enters the distal segment of artery.

The absence of Korotkoff sounds ("no blood pressure") over vessels at a time when direct pressures may be within normal limits is occasionally encountered and such an example is L. S. of table 1. This patient had a very low cardiac output and extreme vasoconstriction of the extremities. His arterial pulse contour showed a brief spike of pressure in systole which reached 150 mm. Hg for .05 sec. and dropped sharply to 90 or 95 mm. Hg. It is likely that this brief pressure rise was damped out by the pneumatic cuff and at the time blood penetrated the compressed segment, the pressure head was not of sufficient magnitude to produce flow adequate for the production of an audible sound.

In truly hypotensive states, the stroke volume entering the aorta may be quickly damped or a weak pulse propagated. Korotkoff sounds may not be heard and a "zero" pressure may be found in spite of measurable values obtained by arterial puncture, because the flow at the time of pulse penetration is below that required for the production of a sound. This situation is the reverse of the audible sounds heard at zero cuff levels (See table 1). It is of interest that exercise or vasodilation of a limb will accentuate the sounds of

Korotkoff. This has been suggested as an indication of the relative amount of blood flow.[7]

Summary

1. The relationships of intravascular pressure to spontaneous and induced sounds heard over arteries have been investigated in 16 subjects with normal hemodynamics or with circulatory relationships altered either by disease or by drugs.

2. It was found consistently that the sounds preceded the rise in pressure. The possible mechanism of this relationship is discussed.

3. It is suggested that such sounds ("pistol-shot" sounds and Korotkoff's sounds) are related to periods of unsteady flow and that these periods occur as the result of rapid changes from one velocity profile to another. This energy is released which manifests itself as sound. Gross quantitation of the amounts of energy involved is attempted.

4. The phenomenon of "pistol-shots" in aortic insufficiency and in states with high cardiac output, the finding of "zero diastolic" cuff readings, and the absence of Korotkoff sounds in the presence of normal or reduced direct pressure values may be explained by the hypothesis presented.

Summario in Interlingua

1. Le relation de pression intravascular con spontanee e inducite sonos audite supra arterias esseva investigate in 16 subjectos con hemodynamica normal o con conditiones circulatori alterate per morbos o drogas.

2. Il esseva constatate que le sonos occurreva regularmente ante augmentos de pression. Es discutite le mechanismo possibile de iste relation.

3. Nos opina que tal sonos (sonos a "colpo de pistola" e sonos de Korotkoff) es relationate a periodos de fluxo instabile e que iste periodos occurre como resultato de rapide transitiones ab un profilo de velocitate a un altere. Le energia assi liberate se manifesta in le forma del sonos. Nos ha tentate un quantitation grosse del energia involvite.

4. Le phenomeno del "colpos de pistola" in insufficientia aortic e in statos con alte rendimentos cardiac, le constatation de lecturas bracial de "zero diastolic," e le absentia de sonos de Korotkoff in le presentia de normal o reducite pressiones directe pote eser explicate per le hypothese formulate in le presente reporto.

Appendix

Although equation 3 gives the general relationship for a change in kinetic energy and the factors involved, it is possible to develop the relationship between radius and kinetic energy assuming some but no striking changes in mean linear velocity. Previous arguments have indicated that systole would possibly have a lower mean velocity than diastole. Consider a lamina of thickness dx of unit length in a vessel of radius R:

where x = *distance from the center*

$dm = \rho 2\pi x\, d\,x$

ρ = *density of the fluid*

dm = *mass of the lamina of unit length.*

then the Kinetic Energy (K.E.) of this lamina, dKE, is:

$$dKE = dm\, v_i^2$$

where v_i is instantaneous velocity (equation 1) From equation 1

$$v_i = (R^2 - x^2)(2\bar{v})$$

$$v_i^2 = 4\bar{v}^2(R^4 - 2R^2x^2 + x^4)$$

$$dKE = [\rho 2\pi x\, d\,x][4\bar{v}^2(R^4 - 2R^2x^2 + x^4)]$$

$KE = \frac{1}{2}mv^2$ or

$$\rho 4\pi\bar{v}^2 \int_0^R (R^4x - 2R^2x^3 + x^5)\, d\,x \quad \text{Equation 4}$$

$$= \rho 4\pi\bar{v}^2 \frac{R^6}{6}$$

$$KE/\textit{unit length} = \frac{2\rho\pi\bar{v}^2R^6}{3} = K\frac{2}{3}\rho\pi R^6$$

where $\bar{v}$ does not change and K is a proportionality constant. From equation 4, and the consideration of the parabolic flow profile, two pertinent relationships are apparent. First, as in the case of W. H., the kinetic energy/unit length of blood changes 27 fold as the radius increases by 1.7. Second, the greatest portion of that increase in energy is contained by the inner two thirds of the systolic column which is in direct flow continuity with the diastolic column (fig. 5).

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The Prevention of Thromboembolic Complications in Myocardial Infarction by Anticoagulant Therapy

A Clinical-Pathologic Study

By HELEN I. GLUECK, M.D., HENRY W. RYDER, M.D., AND PHILIP WASSERMAN, M.D.

Autopsy records of 151 patients dying of acute myocardial infarction, in a large private hospital, were reviewed. Half of the patients received anticoagulant therapy. Hemorrhage was not a significant cause of death in Dicumarol-treated patients. Embolic complications, often undiagnosed clinically, were of common occurrence. Adequate anticoagulant therapy effectively reduced, not only the total number of emboli, but also the number of serious or fatal emboli. In this role, anticoagulants serve a useful purpose in the treatment of myocardial infarction.

EARLY optimism regarding the effectiveness of anticoagulant therapy in patients with myocardial infarction has been tempered by changing concepts of the mortality in this disease, by the risk of hemorrhage attending their use, and by the difficulty in clinical appraisal of any therapeutic agent in a disease characterized by great variability.[1-5] Although thousands of cases are included in the clinical data, with few exceptions autopsy material has not been utilized to study the effects of these drugs.[5-8] It is known that death in myocardial infarction may result from shock, congestive failure, arrhythmia, embolization, or ventricular rupture. These multiple factors influence the prognosis of the patient in diverse ways so that a clinical appraisal of one factor, thromboembolism, and its role in mortality and morbidity has been difficult to assess. With reliance solely on clinical data, it is even more difficult to determine the efficacy of anticoagulant therapy in preventing these complications of myocardial infarction. The present series of autopsied cases demonstrates the importance of thromboembolic complications as a cause of death in myocardial infarction, gives quantitative evidence of the value of anticoagulant therapy in preventing these complications and indicates how slight is the risk of hemorrhage subsequent to their utilization.

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MATERIAL AND METHODS

The present series of 151 autopsied cases was collected from a private general hospital with an active service in cardiovascular disease. All records were obtained from patients admitted between January 1, 1946, and December 31, 1953, inclusive. This eight-year period was selected for 2 reasons: first, records classified by the "unit" system were easily obtained, and second, during this interval a standard anticoagulant data sheet had been utilized for all patients receiving the drugs. The daily dosage, the prothrombin response, and the complications of therapy were thus clearly indicated on all records.

The clinical diagnosis of myocardial infarction was made in 960 instances during this period. This figure included, not only those dying shortly after admission, but also those dead on arrival to the hospital in whom the diagnosis was often presumptive. Of the patients admitted with this diagnosis 316 (32 per cent) died and 193 autopsy records (61 per cent) were available. Forty-two records were discarded because the patient had survived in the hospital less than 24 hours and the data were therefore incomplete. One hundred fifty-one suitable records otherwise unselected were thus available for study.

Medical care was largely directed by private physicians, among whom internists predominated

TABLE 1.—*Final Clinical Diagnosis on 151 Autopsied Patients with Myocardial Infarction Classified with Regard to the Use of Anticoagulant Therapy*

		No. of Cases
1. Anticoagulant therapy ("treated")	(76)*	
A. Infarct diagnosed clinically	(72)	
B. Infarct not diagnosed clinically	(4)	
Final clinical diagnosis:		
Congestive failure		1
Cerebrovascular accident		3
2. No anticoagulant therapy ("untreated")	(75)	
A. Infarct diagnosed clinically	(49)	
Reasons for omission of drug:		
Years before general use of drug		16
Diagnosis late or uncertain		14
No stated reason		5
Associated cerebral symptoms		3
Recent ulcer		3
Doctor or patient refusal		3
Surgery contemplated		3
Renal disease, uremia		2
B. Infarct not diagnosed clinically	(26)	
Final clinical diagnosis:		
Congestive failure		8
Cerebrovascular accident		8
Pneumonia		3
Miscellaneous		7†

* In parenthesis, total number in that category.

† Generalized vascular sclerosis, gastric hemorrhage, ruptured ventricle, ruptured aneurysm, diabetes, uremia, pulmonary emboli.

Seventy-six per cent of patients receiving the drugs, as well as 76 per cent of those not given anticoagulant therapy, were attended by internists. The remainder of the patients in both groups were seen either by general practitioners or on the service wards of the hospital. Consultation was widely used in the latter two categories.

Autopsies were performed by or under the direction of two senior pathologists,* thus insuring uniform interpretation of pathologic material. For the most part, the autopsies were completed independent of the present investigation, so that the pathologic findings were unbiased by the present study.

* Dr. Philip Wasserman, Director, Department of Pathology, Jewish Hospital Association, and Dr. Jan Schwartz, Associate Director, Department of Pathology, Jewish Hospital Association.

CHARACTER OF THE SAMPLE—CLINICAL ANALYSIS

The final clinical discharge diagnoses at death are summarized in table 1. Seventy-six patients receiving any form of anticoagulant therapy were included in the "treated" group. The "untreated" consisted of 75 in whom no such drugs were administered.† A discrepancy existed between the clinical and pathologic diagnosis in 26 of the "untreated" and 4 of the "treated" patients. Since the diagnoses were often more obscure in the "untreated" group, it is clear that the two groups were not selected completely at random ($P = <.001$).[9] Nevertheless, it is possible to compare the groups in a number of their clinical and pathologic attributes, once these differences in the samples are recognized.

The clinical features of the two groups are presented in table 2. The two groups were similar in regard to age, race, sex, obesity, the presence of failure, arrhythmia, history of previous occlusion, and the finding of shock. The mean age of the "treated" group was 62.2 years, of the "untreated" 64.9. Figure 1 shows the similar age distribution of the two groups by three-year intervals. A high incidence of failure characterized both groups (table 2). Serious arrhythmias were likewise of common occurrence in both groups (table 2). These included atrial fibrillation or flutter, frequent atrial or ventricular extrasystoles, various degrees of heart block, and ventricular tachycardia or fibrillation.

The duration of illness from onset of symptoms to death is plotted in figure 2. Twenty-two patients in whom emboli were a primary cause of death, or a major contributing cause of death (as determined by pathologic study) have been plotted separately. Six of these deaths occurred in "treated" patients, 16 in "untreated" patients. The time-mortality curves for the three groups are similar. By the tenth day of hospitalization half of all the

† The similarity in numbers of the 2 groups is fortuitous. The study was terminated in 1953, since anticoagulant therapy is at present almost routinely used, thus limiting the number of "untreated" patients.

TABLE 2.—*Clinical Comparison of "Treated" and "Untreated" Groups, Classified with Regard to Clinical Characteristics and Statistical Significance*

	"Treated" 76 Patients	"Untreated" 75 Patients	P*
A. Differences Not Statistically Significant			
Age in years, mean	62.2	64.9	
Race (Jewish)	25	22	
Obesity	15	10	
Congestive failure			
Present on admission	46	31	
Developed	10	15	
	56	46	
Major arrhythmia			
Present on admission	7	5	
Developed	9	8	
	16	13	
Shock			
Present on admission	12	13	
Developed	17	23	
	29	36	
Previous occlusion	22	17	
B. Differences Statistically Significant			
Sex (male)	54	35	.01–.001
Diabetes	10	23	~.01
Hypertension (history or finding on admission)	35	53	.01–.001
Angina	36	18	.01–.001

* P = probability of the chance occurrence of such distributions, calculated from χ^2.[9]

deaths had occurred. Patients who survived were usually hospitalized for 4 to 6 weeks. This period of observation was sufficiently long for serious late complications to be included in the pathologic material.

Significant differences were noted in the "treated" and "untreated" groups in regard to sex, diabetes, hypertension, and angina (table 2). Their confirmation by pathologic data and their role in the patients' deaths are considered.

ADEQUACY OF ANTICOAGULANT THERAPY

It was observed early in the study that certain of the "treated" patients had received only "token" anticoagulant therapy. An occasional patient had received only 1 or 2 doses of the drugs during 10 or more days. Others

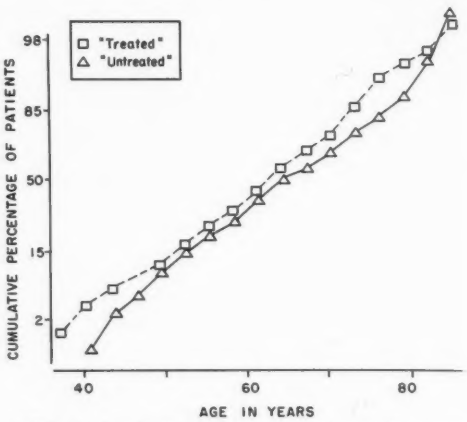

FIG. 1. Age in "treated" and "untreated" groups. The cumulative plot is of the age at the midpoint of each 3 year class interval. The ordinate, percentage, is on a probit scale.

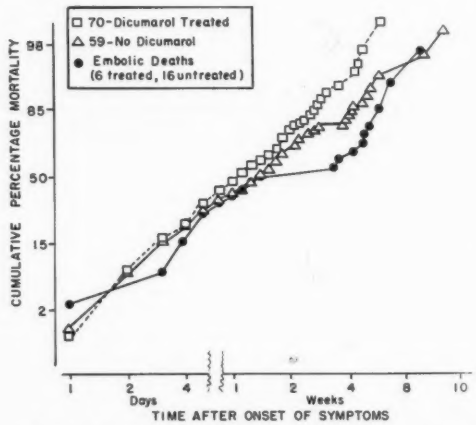

FIG. 2. Time-mortality curve in "treated" and "untreated" groups. The patients in both groups dying of emboli (6 "treated", 16 "untreated") are plotted separately. The ordinate, percentage, is on a probit scale.

had received small, inadequate dosage. In order to define therapy as "adequate," certain arbitrary criteria were established. In general, they correspond to those of Wright and the group of the American Heart Association.[5] These criteria for adequacy are as follows:

1. Initiation of anticoagulant therapy not later than six days after the onset of symptoms suggesting myocardial infarction.
2. At least 21 days of therapy.

3. Prothrombin concentration of 30 per cent or less (Quick assay) at least 70 per cent of the time dicumarol was administered, excluding the first 5 days of therapy.

All but 2 of the patients in this series received heparin by various routes at the onset of treatment, along with dicumarol. Heparin was continued until the prothrombin concentration had fallen to 30 per cent or less of the normal concentration. One patient received phenindione (Hedulin). Of the 76 patients receiving anticoagulants, 56 had adequate therapy when classified by the above criteria.

Character of the Sample—Pathologic Analysis

The primary cause of death as classified by the pathologist is noted in table 3. All 151 patients died with myocardial infarction, although secondary causes, for example, failure or shock, were often immediately responsible for the patient's death. On pathologic examination, many of the clinical differences between the 2 groups could not be confirmed. Congestive failure occurred in 66 of the "treated" and 68 of the "untreated" group (table 4). Although a portion of the failure might be ascribed to terminal pulmonary edema, the incidence of failure was higher in both groups than the clinical data had suggested.

Clinically, hypertension was commoner in the "treated" group. Cardiac hypertrophy however, one objective reflection of sustained hypertension, was of equal distribution in both groups (fig. 3). Likewise the incidence of a previous occlusion was greater in both groups than the history had indicated, since it was found at autopsy in 30 of the "treated" and 27 of the "untreated" patients.

Aneurysmal dilatation of the left ventricle resulting from a previous infarct was found in 5 of the "untreated" and in 12 of the "treated" patients ($P = .1–.05$). Old mural thrombi in association with the aneurysm were found in 3 of the former and 7 of the latter categories, which confirm the findings of Schlichter, Helpstein, and Katz regarding the frequency of this complication in patients with myocardial infarction.[10]

A definite thrombotic coronary occlusion was found on gross examination in 61 patients in the "untreated" and 64 of the "treated" group. Myocardial infarction without thrombosis was noted in 14 of the "untreated" and 12 of the "treated" patients. The left coronary artery was thrombosed in 27 of the "treated" and 25 of the "untreated" patients, the right artery in 8 of the "untreated" and 9 of the "treated" patients. Thrombosis was noted in the circumflex artery in 8 "untreated" and 4

Table 3.—*Pathologic Diagnosis of the Primary Cause of Death in 151 Patients Dying with Acute Myocardial Infarction*

	"Treated" 76 Patients	"Untreated" 75 Patients	*P*
A. Differences Not Statistically Significant			
Myocardial infarction*	53	42	
Ruptured ventricle	6	5	
Cerebrovascular accident	1	5	
Congestive failure	6	4	
Pneumonia	1	2	
Pyelonephritis (chronic)	1		
Perforated duodenal ulcer		1	
Multiple hemorrhages	1		
B. Differences Statistically Significant			
Emboli	7†	16	.02–.01

* In the cases listed as myocardial infarction the pathologist could find no other immediate cause of death. In the remainder of the cases, the causes listed were considered the primary factor precipitating death, even though often consequent to the infarct.

† Of these 7 patients in the "treated" category, 5 received inadequate anticoagulant therapy. Excluding these patients, $P = .0025$.

Table 4.—*Pathologic Observations on Congestive Failure in 151 Autopsied Patients with Myocardial Infarction*

	"Treated"	"Untreated"
Pulmonary congestion	38	34
Pulmonary edema	10	3
Right-sided failure	3	7
Combined—right and left	15	24
No failure	10	7
Total	76	75

Differences are not statistically significant.

TABLE 5.—*Chamber Involvement by Mural Thrombi in 151 Patients with Myocardial Infarction, Classified by Treatment Categories and Number of Chambers Involved*

		None	One	More Than 1
"Treated" adequately...	(56)	43	10	3
"Treated" inadequately.	(20)	8	7	5
"Untreated".....	(75)	44	19	12

In parentheses are the number of patients in that category. When only the presence or absence of mural thrombosis is considered, the probability is between .01–.001 that the differences in the three groups are due to chance alone.

TABLE 6.—*Embolization in 151 Patients with Myocardial Infarction, Classified by Treatment Categories, Number of Emboli Per Patient, and Significance of the Emboli*

		Number of Emboli Per Patient			"Primary"*
		None	One	More than one	
"Treated" adequately...	(56)	51	4	1	2
"Treated" inadequately.	(20)	11	5	4	5
"Untreated".....	(75)	44	14	17	16

In parentheses are the number of patients in that treatment category.

When only the presence or absence of embolization is considered, the probability is less than .001 that the differences in the three groups are due to chance alone.

* "Primary"—emboli as a primary cause of death or major contributing cause of death. (See text.) The probability is between .01 and .001 that the differences in the 3 groups are due to chance alone.

"treated" patients. The remainder of the coronary thrombi were found in various combinations.

THROMBOEMBOLIC COMPLICATIONS AS AFFECTED BY ANTICOAGULANT THERAPY

Mural Thrombi

Mural thrombi, visible grossly, were significantly reduced by adequate therapy. They were present in 13 of the "adequately treated" group, while 31 in the "untreated" group showed this complication. Inadequate therapy, however, was of no advantage, since mural thrombi were found in 12 of 20 "inadequately treated" patients (table 5). In the "adequately

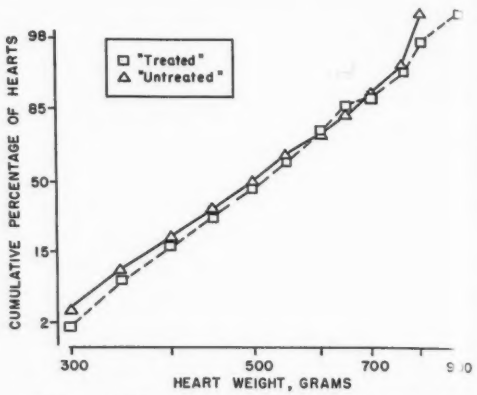

FIG. 3. Heart weight in "treated" and "untreated" groups. The cumulative plot is of the weight at the midpoint of each 50 Gm. interval. The abscissa scale is logarithmic. The ordinate, percentage, is on a probit scale.

treated" group, more than 1 chamber was involved in 3 cases, whereas there were 19 such instances in the "untreated" group (table 5).

The early appearance of mural thrombi is noteworthy, occurring in a number of patients whose clinical history was brief. Twenty-two patients receiving adequate anticoagulant therapy died on or before the fifth day of illness (fig. 2); mural thrombi were present in 5 of them. Nineteen of the "untreated" group died in this same interval; mural thrombi were present in 7. Mural thrombi were present in 2 of 6 "inadequately treated" patients dying during this same period.

Emboli

A striking reduction in emboli was observed in the present series of patients receiving anticoagulant drugs. In the "untreated" group, 31 instances of such complications were noted (41 per cent); among "adequately treated" patients, 5 were found (9 per cent) (table 6). Inadequate therapy was of no noticeable advantage when compared with the "untreated" group, since 9 such patients (45 per cent) were found with emboli.

Adequate anticoagulant therapy not only prevented emboli, but if emboli were present, they occurred in fewer numbers. In the "adequately treated" group, only 1 patient had emboli in more than 1 site, while 17 such in-

stances were found in the "untreated" group. Again inadequate therapy offered no advantage (table 6), 85 embolic sites being found in the "untreated" group, whereas only 6 were observed in "adequately treated" patients. The diminution in the number of emboli is important, since widely scattered, multiple emboli have a serious prognosis.

Emboli as a Major Contributing Cause of Death

The significance of the emboli in relation to the death of the patient was studied. Cases were selected in which the pathologist classified the emboli at the time of autopsy, as "primary cause of death" or "major contributing cause of death." Sixteen such patients were found in the "untreated" group (21 per cent), whereas only 2 were observed in the "adequately treated" patients (3 per cent) (table 6). Considered as an important cause of death were massive, repeated or multiple pulmonary infarcts, venous thrombosis associated with massive pulmonary infarction, extensive cerebral thrombosis or infarction, peripheral arterial or mesenteric occlusion, and multiple emboli in scattered areas. As was previously observed in regard to the number of patients affected with emboli, inadequate therapy offered no protection against this complication.

Age of Patient and Occurrence of Emboli

The relationship of age and the incidence of embolization is seen in figure 4. There was a higher incidence of emboli in patients 60 years of age and over, particularly in the "untreated" group. The diagram illustrates the marked diminution in embolic phenomena in this age group when anticoagulants were used. There were, however, 47 patients under 60 years of age in the entire group of patients studied. In these 47 patients, 10 showed emboli (21 per cent). Only 1 of the 10 patients of this combined group had received adequate anticoagulant therapy.

The Clinical Diagnosis of Embolism

The present study emphasizes the difficulty in the clinical diagnosis of emboli as recently shown by Towbin[11] and others.[5] The clinical diagnosis of embolism was made only 7 times

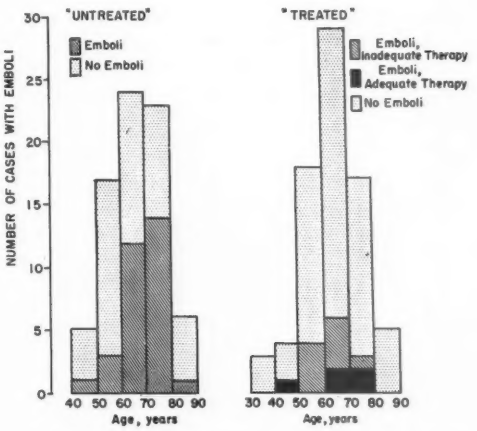

FIG. 4. Relation of emboli to the age of the patient. The ages are plotted by decades at the end of each class interval. The number of patients in each group is plotted on the ordinate.

in the "untreated" group, whereas 31 patients were found with this complication. In the "treated" group the diagnosis was correctly made in 5 of the 15 patients in whom emboli were found at autopsy. The diagnosis was usually correct when cerebrovascular or peripheral arterial occlusion occurred. Pulmonary emboli, however, were often overlooked clinically, even when obvious on gross dissection. The diagnosis was even more difficult in the presence of multiple emboli.

Cerebrovascular Accidents and Myocardial Infarction

In 8 of the "untreated" and 3 of the "treated" patients (table 1) cerebrovascular accidents obscured the diagnosis of myocardial infarction. The common association of these 2 disorders as emphasized by Bean[12] adds further difficulty in the diagnosis of myocardial infarction.

Thromboembolic Complications as Influenced by the Characteristic of the Sample

The greater incidence of emboli observed in the "untreated" group could not be ascribed to differences in the 2 groups in regard to sex, clinical history of hypertension, and diabetes (Appendix A, B, C, table 1). Emboli were less

common in the "untreated" group with a history of angina (Appendix D, table 1). No association of age, sex, diabetes, or mural thrombi in these "untreated" patients with a history of angina could explain this difference (Appendix, table 2). It is possible that the subjective history of angina in this group of acutely ill patients was unreliable.

Extension of Infarct or New Infarct

Four patients in the "untreated" group showed either extension of a fresh infarct upon an older infarct or a completely new infarct in association with an older one, in either case suggesting a recent extension of the coronary thrombosis with further vascular occlusion. Five of the "treated" group (4 on adequate dicumarol therapy) showed similar extension. In every instance, whether or not the patient received anticoagulant drugs, extension was always associated with profound calcification of the arteries, the lumina often being so narrowed as to be imperceptible on dissection.

Thrombophlebitis

The venous channels of the legs are a well-known focus of emboli in patients with myocardial infarction.[13] Although dissection of the calf veins was not carried out in the present study, 6 of the patients in the "untreated" group (8 per cent) had thrombosis of the inferior vena cava or the iliac veins. No instance of thrombosis of these vessels was found in the "treated" group (P = .01–.001).[14] In 5 of the 6 patients with venous thrombosis, multiple or massive pulmonary emboli were found at autopsy. Anticoagulants seemed highly effective in preventing thrombophlebitis and subsequent disastrous emboli.

Complications of Therapy: Hemorrhage, Ruptured Ventricle, and Hemorrhagic Pericarditis

Table 7 summarizes the data in regard to hemorrhage. Of interest was the occurrence of hemorrhage in the "untreated" group. At autopsy, 5 (6.6 per cent) of the "untreated" group showed gross evidence of hemorrhage, while a sixth had severe nosebleeds when alive. Serious significance was ascribed to hemorrhage from duodenal ulcer in 1 of the "untreated" patients, and to a cerebral hemorrhage in a second. Seven of the patients receiving dicumarol (9.2 per cent) showed evidence of gross hemorrhage. In 1 patient with gastric bleeding and a second with gross hematuria, the diagnosis was made clinically, and the drugs were discontinued. Microscopic hematuria often occurred with adequate anticoagulant therapy and was not regarded as a contraindication to the drug. Death was ascribed to hemorrhage in 1 "treated" patient. Massive bleeding was noted in the medulla, the large and small bowel, and the bladder. These hemorrhages were not detected clinically, nor was the prothrombin concentration excessively low during life. There is no statistical significance between the occurrence of hemorrhage in the "untreated" and "treated" group.

TABLE 7.—*Incidence and Site of Hemorrhage in 151 Patients Dying with Myocardial Infarction, Classified by Treatment Categories*

Site of Hemorrhage	"Treated"	"Untreated"
Esophagus	1	1
Gastritis or superficial ulceration	2	1
Duodenal ulcer	1	1
Pulmonary infarcted areas	1	1
Renal	1	
Cerebral (gross hemorrhage)	1	1
Multiple—large bowel, small bowel, medulla, bladder	1*	
Ruptured ventricle	6	5
Hemorrhagic pericarditis	1	1
Fibrinous pericarditis	7	2

* Responsible for patient's death.
None of the differences is statistically significant.

Five patients in the "untreated" group (6.6 per cent) and 6 receiving dicumarol (7.9 per cent) died with rupture of the left ventricle. One patient in each group was found to have hemorrhagic pericarditis without obvious rupture. A higher incidence of fibrinous pericarditis without gross hemorrhage or rupture, however, was found in the "treated" group, 7 such instances being found in the "treated" group, while 2 were found in the "untreated" (P = .1–.05).

DISCUSSION

The 2 groups were similar in regard to age, heart weight, and duration of illness. There

were likewise no significant differences in regard to race, obesity, congestive failure, major arrhythmia, shock, previous infarction, extension of infarction, aneurysmal dilatation of the ventricles, or hemorrhage. Excluding emboli, the primary causes of death were similar in the 2 groups. Furthermore, even though there were observed differences in regard to sex, diabetes, and history of hypertension, the effectiveness of anticoagulant therapy in reducing embolic complications was not modified by these differences. We assume that the association between angina and diminution in emboli was fortuitous.

The incidence of thromboembolic complications in the 2 groups stands in sharp contrast to these fundamental similarities. The total number of emboli, the incidence of emboli as a primary cause of death, and the incidence of mural thrombosis were all reduced by adequate specific therapy until they were no longer major factors in the over-all mortality.

The present series of autopsied patients emphasizes the observation that patients seriously ill with myocardial infarction are prone to thromboembolic complications. These data confirm the observations of Hellerstein and Martin,[15] who studied a group of autopsied patients not receiving dicumarol. They found an incidence of 26 per cent serious or fatal emboli. Miller and co-authors,[16] studied a similar group and found fatal thromboembolic complications in 14 per cent of their cases. In the collected autopsy series of Wright, Marple, and Beck[5] the extra cardiac complications of myocardial infarction were reduced from 125 per 100 cases in the "untreated" to 45 per 100 patients given anticoagulants. Burton[6] noted a reduction in emboli from 62 per cent of the "untreated" to 10 per cent of the "treated" cases. Gilchrist and Tulloch[8] found thromboembolic complications 2¾ more frequent in the "untreated" than the "treated" group. In the present series, not only were the total number of patients affected by emboli reduced with anticoagulants, but also the incidence of fatal or serious emboli was markedly diminished.

The present study indicates that anticoagulant therapy must be started early and used adequately in order to be effective. Inadequate, poorly planned therapy is no more effective in preventing emboli than no therapy whatsoever. The time-mortality curve of fatal embolization, the findings of fresh mural thrombi by the fifth day of symptoms, and the occurrence of aneurysms containing old mural thrombi forming a nidus for propagation of a new thrombosis, emphasize the urgency of early anticoagulant therapy. These observations theoretically justify the concomitant use of heparin and dicumarol on the initiation of therapy, since dicumarol is ineffective during the first few days of its use.

There is an undue risk in waiting to make a definitive diagnosis of myocardial infarction in doubtful or dubious cases. It is necessary only to recognize that the patient has a condition in which thromboembolic complications are a real hazard.[17-19] Without question, anticoagulant therapy diminishes the disability and death associated with embolic complications, not only in patients with myocardial infarction, but also those without infarction whose clinical status is otherwise similar.

Russek and co-authors[20, 21] have recommended that patients on admission to the hospital be classified according to "good" or "bad risk" categories, reserving anticoagulant therapy only for the latter group. Schnur[2] has shown that the response to any type of therapy in myocardial infarction, insofar as reduction in mortality is concerned, varies with the severity of the clinical status of the patient rather than the effect of any specific drugs. It is being recognized, however, that the prognosis of the patient cannot be made definitely, especially on admission to the hospital, particularly for the first 48 hours.[22] In the present series many patients shifted from "good risk" to "bad risk" categories (table 2). The pathologic data revealed the difficulties in such rigid clinical classification as well as the difficulty in diagnosing the atypical infarct or myocardial infarction associated with cerebrovascular accidents.

The important condition for the clinician to consider is that the patient has a real risk of developing thromboembolism because of failure, shock, arrhythmia, or prolonged inac-

tivity. A definitive diagnosis of myocardial infarction is not of great moment at this early stage. Yet early treatment is life-saving, since half of the patients with embolic complications die within 10 days of the onset of the symptoms of myocardial infarction.

The difficulty in accurate clinical diagnosis of emboli observed in the present series of cases has been noted by Hellerstein and Martin,[15] Wright and associates,[5] and others. This difficulty must be considered when it is stated that clinically emboli are uncommon in patients with myocardial infarction.[1]

Emboli were more frequent in the present series in patients of older age (fig. 4). Nevertheless emboli were present in every age category, a finding confirmed by others. It is not unexpected, therefore, that the reduction in emboli in the present series and that of Wright and associates[5] was the most striking in patients past 60 years of age. Nevertheless, thromboembolic disease, a hazard at all ages, is largely preventable; youth *per se* therefore should not be a contraindication to the use of the drugs.

In the present series intracardiac mural thrombi were definitely diminished by adequate anticoagulant therapy. Hellerstein and Martin[15] noted mural thrombi in 41 per cent of 160 patients not receiving dicumarol. Jordan et al.[23] found mural thrombi in the left ventricle in 33 per cent of 327 patients. In Bean's series[12] of 300 autopsied patients the incidence was 47 per cent.

The few large series comparing the incidence of mural thrombi in "untreated" patients and those receiving dicumarol, have all shown a reduction in the number of mural thrombi under adequate anticoagulant therapy. Wright and associates[5] found mural thrombi present in 63 per cent of the "untreated" and 33 per cent of the "treated" cases. Burton's series,[6] collected from a single source, showed mural thrombi in 69 per cent of the "untreated" cases and 43 per cent of patients receiving anticoagulant therapy. Howell and Kyser,[7] and Gilchrist and Tullock[8] noted reduction in mural thrombi and subsequent emboli in patients on anticoagulant therapy.

In the present series adequate anticoagulant therapy failed to prevent the extension of the infarct or a new thrombosis in the coronary circulation. In the entire group with this complication, sclerosis was of such intensity that the drug appeared ineffectual. The failure of adequate anticoagulant therapy to prevent extension of infarction in the presence of severe atherosclerosis has been confirmed by the autopsy studies of Wright, Marple, and Beck.[5]

Thrombophlebitis of the venous channels in the extremities was diminished with anticoagulant therapy, no single instance being noted in the "treated" group. Five of the 6 patients with this complication in the "untreated" group had emboli. One of the chief contributions of anticoagulant drugs may well be their effect on venous thromboses, which are so commonly associated with cardiac disease.

The incidence of hemopericardium and rupture was higher in Wright's series of patients receiving dicumarol than in his "untreated" group.[5] Similar observations were made by Waldron and co-authors.[24] Goldstein and Wolff[25] found hemopericardium associated with fibrinous pericarditis in patients receiving dicumarol for myocardial infarction. Anderson and co-workers,[26] however, reported similar findings in 1 patient not receiving dicumarol. Dicumarol has produced hemopericardium when given after myocardial trauma,[27] and in patients with nonspecific pericarditis.[28, 29] In the present series, small areas of focal hemorrhage were usually observed with exudative fibrinous pericarditis. In the 2 cases of frank hemorrhagic pericarditis, however (table 7), the area of fibrinous pericarditis was localized and well circumscribed.

The incidence of hemorrhagic complications is low, in most series.[5, 6] In our opinion the increased risk of hemorrhage, of hemorrhagic pericarditis, and of rupture of the ventricle is less than the benefit to be obtained with the judicious use of these drugs, provided there is adequate laboratory control and clinical awareness of the risk their use entails.

The present communication indicates that the chief purpose of anticoagulant therapy in acute myocardial infarction is the prevention of the thromboembolic disease that often accompanies the infarct. In this role, an i-

coagulant drugs serve a useful purpose largely in controlling this serious complication. Their use should not divert the clinician from the problems of shock, failure, and arrhythmia, which together play a more decisive role in the final outcome of the patient.

Summary

Autopsy records of 151 patients dying of myocardial infarction in a large private hospital were reviewed. Seventy-six patients received anticoagulant therapy, and 75 patients did not. Embolic phenomena were of common occurrence in patients dying with myocardial infarction. Clinically, these were often overlooked. The utilization of anticoagulant drugs reduced strikingly the incidence of embolic complications from 41 per cent in the "untreated" series to 9 per cent in the "adequately treated" group. Emboli responsible for the death of the patient, as judged by the pathologist, were reduced from 21 per cent in the "untreated" group to 4 per cent in patients receiving adequate therapy. Inadequate, delayed or poorly planned therapy afforded the patients no protection from this complication. Thrombophlebitis was markedly diminished in "treated" patients, and fewer mural thrombi were found in patients who received adequate therapy. Extension of the infarct or a new infarct was uninfluenced by anticoagulant drugs.

Hemorrhage in the present series was not a significant cause of death. Rupture of the ventricle was noted to occur in both groups regardless of therapy.

The patients could not be rigidly classified on admission to the hospital in regard to their eventual prognosis. This observation, plus the difficulty of diagnosis and the unpredictability of the disease, confirmed the inference that the decision to use anticoagulant therapy should not be dependent upon rigid diagnostic criteria for infarction. The benefit to be obtained from these drugs during the acute phase of illness can be ascribed to the prevention of thromboembolic complications. The indication for their use is a clinical condition in which thromboembolism is a real hazard. In this role they are a useful adjunct in the treatment of myocardial infarction.

Acknowledgment

We are indebted to Miss Caroline J. Watkins, Record Librarian, for her help in obtaining records; Ruth Slutz gave valuable aid.

Summario in Interlingua

Es revidite le protocollas autoptic de 151 patientes morte ab infarcimento myocardiac in un grande hospital private. Septanta-sex patientes recipeva therapia anticoagulants; 75 non. Phenomenos embolic esseva de occurrentia commun in patientes moriente ab infarcimento myocardiac. Illos escappava frequentemente al observation clinic. Le utilisation de drogas anticoagulante reduceva le frequentia de complicationes embolic frappantemente ab 41 pro cento in le serie "non tractate" a 9 pro cento in le serie "a tractamento adequate." Embolos considerate per le pathologo como responsabile pro le morte del patiente esseva reducite ab 21 pro cento in le gruppo "non tractate" a 4 pro cento in le gruppo "a tractamento adequate." Cursos de therapia inadequate, retardate, o mal planate non protegeva le patiente contra iste complication. Thrombophlebitis esseva marcatemente reducite in patientes "tractate," e minus thrombos mural esseva trovate in patientes qui recipeva therapias adequate. Extension del infarcimento o disveloppamento de un nove infarcimento non esseva influentiate per drogas anticoagulante.

In le presente serie hemorrhagia non esseva un significative causa de morte. Ruptura del ventriculo occurreva in ambe gruppos sin reguardo al uso o non-uso del therapia.

Le patientes non poteva esser classificate strictemente secundo lor ultime prognose al tempore de lor admission al hospital. Iste observation, insimul con le difficultate del diagnose e le inpredicibilitate del morbo, supportava le conclusion que le decision de usar drogas anticoagulante non debe depender de stricte criterios diagnostic pro infarcimento. Le beneficio obtenibile ab iste drogas durante le phase acute del morbo pote esser ascribite al prevention de complicationes thrombo-embolic. Lor uso es indicate si le condition clinic

es de natura a render le disveloppamento de thrombo-embolismo un ver hasardo. In tal casos illos es un utile adjuncto al tractamento de infarcimento myocardiac.

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APPENDIX

TABLE 1.—*Association of Thromboembolism, Treatment Category, and Clinical Characteristics of the Sample*

	Thromboembolism			
	Preesnt	Absent	Present	Absent
	Male		Female	
A. Sex				
"Treated" adequately	4	37	1	14
"Treated" inadequately	7	8	2	3
"Untreated"	11	24	20	20
	Diabetes		No Diabetes	
B. Diabetes				
"Treated" adequately	2	6	3	45
"Treated" inadequately	1	1	8	10
"Untreated"	9	14	22	30
	Hypertension		No Hypertension	
C. Hypertension (History or Finding)				
"Treated" adequately	2	23	3	28
"Treated" inadequately	5	4	4	7
"Untreated"	22	31	9	13
	Angina		No Angina	
D. Angina				
"Treated" adequately	4	23	1	28
"Treated" inadequately	2	7	7	4
"Untreated"	2	16	29	28

TABLE 2.—*Association of Diagnostic Categories, Sex, and Presence or Absence of Angina*

Diagnostic Category	"Treated"		"Untreated"			
			Diagnosis Made		Diagnosis Missed	
Sex	M	F	M	F	M	F
Angina						
Present	25	11	9	7	2	0
Absent	30	10	13	20	10	14

The Physiologic Effect of Contrast Media Used for Angiocardiography

By GEORGE G. ROWE, M.D., JOHN H. HUSTON, M.D., H. TUCHMAN, M.D., GEORGE M. MAXWELL, M.D., ARVIN B. WEINSTEIN, M.D., AND CHARLES W. CRUMPTON, M.D.

The deaths from angiocardiography at Wisconsin General Hospital were reviewed and found to be two per cent of 249 patients. These 5 deaths are reported briefly. Investigation was carried out to determine the hemodynamic effects of contrast substances on 12 dogs. In general, there was a temporary increase in right atrial and pulmonary arterial pressure followed by a rather marked decrease in systemic arterial pressure and tachycardia. The significance of these findings is discussed in relation to shunts within the heart or between the aorta and pulmonary artery.

DEATH following administration of a contrast substance for the purpose of angiocardiography leaves an indelible impression upon the clinician and radiologist. Several investigators have evaluated this problem as related to specific angiocardiographic contrast substances and considerable experimental work has been done. It has been shown that Diodrast in high concentration produces an increase in the heart's force of contraction[1] and an increase in coronary blood flow in the isolated rabbit heart.[2] In dogs, Diodrast given intravenously in doses equivalent to those used in clinical angiocardiography produces a fall in peripheral arterial pressure, a rise in heart rate, an increase in venous pressure and transient changes in the QRS complex and T wave of the electrocardiogram.[3] The permeability of the cerebral vessels to trypan blue is increased in rabbits after the intracarotid injection of Diodrast and petechial hemorrhages may occur in the brain.[4] Convulsions have been produced by intracarotid injection of Diodrast.[1, 5] The injection of Diodrast into peripheral arterial vessels produces dilatation.[1] Investigations in patients given Diodrast have shown a fall in systemic arterial blood pressure[6, 7] and frequent electrocardiographic changes.[7, 8] Neo-iopax in high concentration has been shown to decrease the output of the heart-lung preparation[1] and to depress the isolated rabbit heart.[9] Frequently following this initial depression in cardiac function, there occurred an improvement that went beyond the control level[1, 9] and was attributed to the coronary vasodilatation with increased myocardial blood supply.[1] Respiration increased in rate and amplitude after Neo-iopax, unless the dosage was very high and then depression occurred.[9] When given rapidly through the carotid artery, apnea, convulsions and death could be produced by Neo-iopax.[1] Thrombosis may be produced in vessels into which this substance is injected.[11] In patients undergoing angiocardiography with Neo-iopax, marked hypotension frequently occurs and electrocardiographic irregularities have been reported.[7] Intravenous injection of Urokon, in large doses, produces hyperpnea, vomiting, defecation, convulsions, collapse and sometimes death.[10]

Deaths following angiocardiography are

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The Neo-iopax used in the study was supplied by the Schering Corporation of Bloomfield, New Jersey; Diodrast was given by Winthrop-Stearns, Inc. of New York City; the Mallinckrodt Chemical Works of St. Louis donated the Urokon.

most common in patients with congenital heart disease of the cyanotic variety,[7, 12, 13] and vary greatly in incidence from one individual's experience to another's. Dotter and Jackson[12] reported that, in two large series of angiocardiographic examinations, totaling 2,500 consecutive studies, no deaths occurred. Data collected by these authors[12] from Sweden revealed one death in approximately 450 studies. Morgan reported 6 fatalities in 600 angiocardiograms,[13] Dimond and Gonlubol, 2 deaths in 100 angiocardiograms,[14] and Carnegie,[15] 4 deaths in 172 cases.

Since deaths are more common in patients with cyanosis and since cyanosis due to shunts is dependent upon the dynamics in both right and left sides of the heart, the present study was undertaken to investigate simultaneously the effects of contrast substance on the right and left sides of the heart.

Methods and Materials

All the cases of fatal reaction to angiocardiography in the University Hospitals were reviewed. Four cases who died at the time of angiocardiography or in the succeeding 24 hours were accepted for study. One additional case (number 1), in whom there can be no reasonable doubt concerning the etiologic relation of contrast substance, was included even though death occurred five days after the angiocardiogram.

Angiocardiography is performed in this institution with the patient in the recumbent position. One milliliter of contrast substance is given intravenously as a sensitivity test and the procedure is completed only if no adverse reaction occurs. When required, a minimal effective concentration of anesthetic agent is given by the open-drop method. Angiocardiograms have been performed 283 times in 249 patients with 5 deaths apparently resulting from the procedure. Neo-iopax is the substance customarily used in this hospital and was used in all the fatal cases. The fatalities occurred in 3 patients with atrial septal defects, (one isolated and 2 complicated), one with rheumatic mitral disease, and one with tetralogy of Fallot. Regardless of the outcome, injection of the radiopaque material frequently produces a profound reaction characterized by cutaneous flushing, tachycardia, and a varying period of apnea followed by hyperpnea. In case 1 this reaction was quantitated by determining pulmonary and brachial artery pressures during the angiocardiogram. A brief summary of each fatal case is appended.

In the experimental study 12 mongrel dogs weighing 8 to 24 kilograms were anesthetized with 3 mg./Kg. of morphine followed, in one hour, by 12 mg./Kg. of sodium pentobarbital. The external jugular vein was exposed and Goodale-Lubin cardiac catheters were inserted into the right atrium and the pulmonary artery. A needle was placed in the femoral artery and a cannula was tied in a peripheral vein of an anterior extremity. The blood pressures were transmitted through short flexible plastic tubes to Statham strain gages and recorded by the Sanborn Poly-Viso. Simultaneous pressures were recorded from the pulmonary artery, right atrium and femoral artery. Mean blood pressures were determined by planimetric integration of the pressure tracings. An electrocardiogram was recorded continuously during the experimental study. After a short control observation, each dog was given 1 ml./Kg. of physiologic saline solution, 75 per cent Neo-opax, 70 per cent Diodrast or 70 per cent Urokoni rapidly intravenously. Each of these agents was administered, after the total demonstrable effect of the preceding injection was completed. Use of each of these agents in each animal is believed important, since the response is, to a degree, an individual matter; being either more or less pronounced to all substances in certain animals. The sequence of administration of the four substances was varied from animal to animal in an attempt to minimize any influence of a prior injection on the effect of each substance. A limited number of observations were made with the injection of contrast substance into the pulmonary artery through a no. 9 cardiac catheter. In an attempt to find a control for effects due to the viscosity of the contrast substances, observations were made following the injection of 1 ml./Kg. of 50 per cent glucose into the pulmonary artery in 2 dogs. Even though the viscosity of all these substances may not be identical, for this purpose they seemed similar enough and the pharmacologic effect of 50 per cent glucose is certainly most evident after its passage through the great vessels and dissemination in body tissues.

Results

The results of the experimental study are summarized in table 1 and diagrammed in figure 3. Figure 1 illustrates a mild response to the injection of Neo-iopax into a peripheral vein and figure 2, a more pronounced response with nodal bradycardia on injection of Neo-iopax through a cardiac catheter into the pulmonary artery.

The administration of saline solution produced no significant changes. All contrast substances, however, produced rather marked responses that were similar but less pronounced, when injection was in a peripheral vein, compared with Neo-iopax injection into

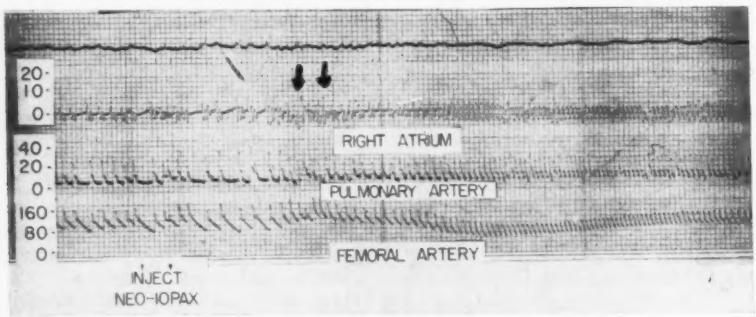

FIG. 1. This tracing shows a rather mild response to injection of 1 ml./Kg. Neo-iopax into the peripheral vein of a dog. Planimetric integration of the area beneath the pressure curve revealed no significant change in right atrial pressure possibly because of the effects of inspiration indicated by the arrows. The pulmonary arterial mean pressure rose from 10 mm. Hg to 13 in 10 seconds, then to 14 in 25 seconds and finally returned to 11 mm. Hg at 70 seconds and 3 minutes. Changes in systemic arterial pressure are obvious to the unaided eye.

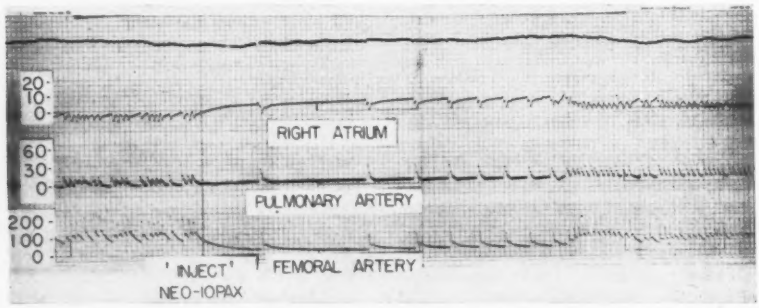

FIG. 2. A much more pronounced change produced by injection of 1 ml./Kg. of Neo-iopax into the pulmonary artery of a dog. The electrocardiogram, upper line, revealed a sinus pause followed by a ventricular premature contraction, several nodal beats and return to sinus rhythm. The dynamic effects on pressure are clearly revealed.

the pulmonary artery. In 2 dogs with surgically created, atrial septal defects, the hemodynamic responses did not differ from those of normal animals.

The cardiac rate generally slowed transiently shortly after administration of the substance, then accelerated significantly ($p < 0.05$–< 0.01) to a maximum in 25 to 70 seconds; over an interval of several minutes, it returned to the control level. The slowing was variable and frequently of such short duration (several beats) that the rate counted over 10 seconds did not decrease significantly. In some instances, marked bradycardia with nodal rhythm occurred almost immediately. This response seemed to be an individual variation, and tended to be reproducible in the dogs in which it occurred.

The usual effect on respiration was marked hyperpnea, which produced inspiratory decreases in the right atrial pressure. In spite of this respiratory effect, the average mean right atrial pressure was elevated 0.4 to 1.0 mm. after the injection of the contrast substances and fell during the following three minutes to the control level in most instances. The right atrial pressure fell 0.2 to 0.9 mm. Hg in five instances, remained unchanged in 2 cases, and rose 0.2 to 7.6 mm. Hg (average +1.7 mm. Hg) in 32 instances (82 per cent). The most significant datum, the true relation of right to left atrial pressure, is not shown. Since, normally, all intracardiac pressures are decreased during deep inspiration, small rises in right atrial pressure or even failure to fall, may be significant under these circumstances.

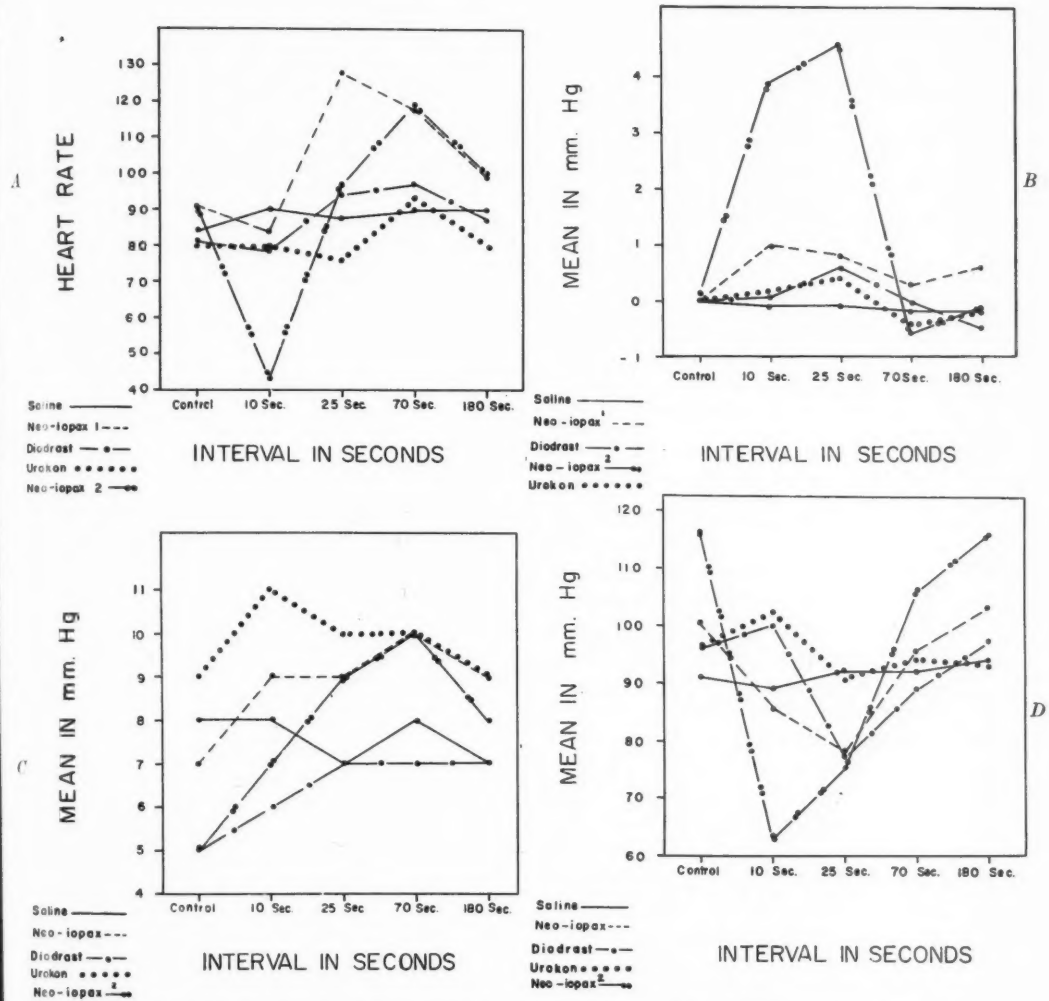

FIG. 3. Effect of contrast substance on *A*, heart rate; *B*, mean right atrial pressure; *C*, mean pulmonary arterial pressure; *D*, mean femoral arterial pressure. Graphs of the responses shown in table 1. Neo-iopax was injected into a peripheral vein and into the pulmonary artery, with a more marked response to delivery into the pulmonary artery.

The pulmonary artery pressure was subject to similar respiratory variation, but showed statistically significant elevation ($p < 0.05$–< 0.01) subsequent to administration of each of the contrast substances. An increase occurred in each instance, the range being +1 to +11 mm. Hg, with an average of +4 mm. Hg. This elevation occurred slightly after that of right atrial pressure and often had not returned to the control level by the end of the three minute period of continual pressure recording. This should be compared to the pulmonary arterial pressure response in case 1, whose systolic rose 27 mm. Hg and whose diastolic rose 20 mm. Hg.

Femoral arterial pressure, on the other hand, showed no change during the early postinjection phase. A considerable fall in peripheral

TABLE 1.—*Hemodynamic Response to Injection of Contrast Substances in Dogs*

Substance Injected		Heart Rate					Mean Right Atrial Pressure (mm. Hg)					Mean Pulmonary Artery Pressure (mm. Hg)					Mean Femoral Artery Pressure (mm. Hg)				
		Control	10 sec.	25 sec.	70 sec.	3 min.	Control	10 sec.	25 sec.	70 sec.	3 min.	Control	10 sec.	25 sec.	70 sec.	3 min.	Control	10 sec.	25 sec.	70 sec.	3 min.
Saline*	Ave.	84	90	88	90	90	−0.9	−1.0	−1.0	−1.1	−1.1	8	8	7	8	7	91	89	92	92	94
8 obs. in 8 dogs‡	S.D.	±31	±28	±30	±33	±34	±1.3	±0.9	±1.1	±1.1	±0.8	±3	±3	±3	±3	±3	±15	±17	±15	±16	±18
Neo-iopax*	Ave.	91	84	128§	118§	99	−2.5	−1.5	−1.7	−2.2	−1.9	7	9§	9§	10§	9°	100	86	78§	96	103
12 obs. in 12 dogs‡	S.D.	±38	±41	±32	±34	±36	±2.1	±1.7	±1.3	±1.6	±1.6	±4	±4	±3	±4	±3	±19	±28	±22	±21	±18
Diodrast*	Ave.	81	79	94‖	97§	87	−1.2	−1.1	−0.6	−1.2	−1.7	5	6§	7§	7§	7‖	96	100	77§	89	97
9 obs. in 7 dogs‡	S.D.	±21	±17	±24	±19	±22	±1.7	±2.1	±2.3	±1.7	±2.0	±1.8	±2.1	±2.6	±2.5	±3.3	±11	±8	±18	±10	±11
Urokon*	Ave.	80	80	76	94°	80	−1.3	−1.1	−0.9	−1.7	−1.5	9	11°	10	10	9	96	102	91	94	93
6 obs. in 3 dogs‡	S.D.	±35	±28	±26	±30	±25	±1.4	±1.7	±1.3	±1.1	±1.2	±1	±2.5	±1.8	±1.7	±1.3	±9	±17	±17	±15	±14
Neo-iopax†	Ave.	91	43	97	119°	100	−1.8	+2.1°	+2.8°	−2.3	−1.9	5	7°	9°	10°	8°	116	63§	75°	106	116
6 obs. in 3 dogs*	S.D.	±36	±14	±60	±29	±20	±2.6	±3.2	±3.1	±3.4	±2.1	±7	±6	±7	±10	±8	±26	±19	±34	±23	±25

* Injected into peripheral vein.
† Injected into pulmonary artery.
‡ Number of observations and number of dogs.
§ = $p < 0.01$.
‖ = $p < 0.02$.
° = $p < 0.05$.

arterial pressure occurred at approximately 25 seconds, accompanied with, and followed by, persisting tachycardia. Because the peripheral arterial pressure did not always return to normal by the end of the three minutes, it was sometimes necessary to delay the next injection until pulmonary and systemic artery pressure returned to the control levels. These changes in right atrial and pulmonary artery pressures were similar with injection of 50 per cent glucose, and are therefore attributed, at least partially, to the physical characteristics of the solution. In one instance, rapid administration of 50 per cent glucose into the pulmonary artery produced transient nodal bradycardia. The 50 per cent glucose produced no remarkable effect on peripheral arterial pressure, the hypotensive changes produced by the contrast substances are therefore presumed to be a pharmacologic effect.

CASE REPORTS

Case 1. This 50 year old woman was admitted to the hospital for consideration of mitral valvulotomy. A heart murmur and mild exertional dyspnea had been present for 30 years, but progressive congestive failure began six months prior to hospitalization. Physical examination revealed moderately severe congestive failure and cardiomegaly with systolic and diastolic apical murmurs. The electrocardiogram showed right ventricular hypertrophy.

Subsequent to therapy with relief of the congestive failure, cardiac catheterization with a no. 9 catheter revealed the pulmonary artery pressure to be 115/52 and the mean "wedge" pressure 25 mm. Hg. Through this catheter 40 ml. of 75 per cent Neo-ipoax was injected manually as rapidly as possible into the right pulmonary artery in an attempt to outline the left side of the heart without overlying right-sided opacification. An immediate severe reaction occurred with cough, dyspnea, tachycardia, and marked apprehension. The brachial artery pressure (directly recorded) fell from 116/77 to 54/36 and then rose to 160/116, while the pulmonary artery pressure fell from 120/53 to 87/67 and then rose to 147/73. With coughing the pulmonary artery systolic pressure exceeded 210 mm. Hg. One hundred per cent oxygen therapy was immediately administered, but progressive dyspnea continued. Numerous rales in the right lung were noted followed by signs of consolidation and a friction rub over the right lower lobe. The angiocardiogram showed the Neo-iopax to remain in the right pulmonary artery throughout the 20 second sequence of films. A subsequent chest film showed massive edema of the right lung with congestion of the left lung unchanged from its appearance prior to catheterization. The patient's course was that of progressive deterioration and she died five days after angiocardiography.

At postmortem examination, the right lung weighed 1,450 Gm. and there was a diffuse fibrinous exudate overlying the hemorrhagically infarcted upper, middle and lower lobes. The heart weighed 380 Gm. The pericardium over the right atrium showed a fibrinous deposit that was seen to overlie an antemortem thrombus. Near the clot in the right atrium was a small round subintimal hemorrhage. The right ventricular myocardium measured 0.5 cm. in thickness and the left 1.5 cm. Atherosclerotic plaques were present in the pulmonary artery. The mitral valve was a rigid, calcific slit 12 mm. long and 2 mm. wide with calcium extending from the

valve into the chordae tendineae and papillary muscles.

Case 2. A 12 month old, 15 pound white female, admitted to the hospital for diagnostic evaluation of congenital heart disease thought to be an atrial septal defect. She had had repeated respiratory infections but no cyanosis. Physical examination revealed bulging of the precordium with a well-marked bilateral Harrison's sulcus. The cardiac impulse was 1 cm. outside the midclavicular line and a systolic thrill was palpable near the third left chondrosternal junction. A harsh systolic murmur was heard over the entire precordium with transmission to the left axilla and the interscapular region.

Cardiac fluoroscopy revealed that the heart was enlarged, the enlargement being predominantly of the right chambers with elevation of the apex above the diaphragm. Pulmonary vascularity was increased. The clinical diagnosis was congenital heart disease with a left-to-right shunt, but the location of this shunt could not be identified.

Angiocardiography was done without difficulty under vinyl ether anesthesia, using 10 ml. of 75 per cent Neo-iopax. The patient was permitted to awaken from anesthesia. The films were not satisfactory, however. Thirty minutes later anesthesia with vinyl ether was reinduced and a second angiocardiogram was performed using 14 ml. of Neo-iopax. Respiration ceased almost immediately after injection of the contrast substance and no pulse could be found. Although artificial respiration was given, the patient did not recover.

Permission for postmortem examination was not granted. The angiocardiogram was interpreted as being compatible with an atrial septal defect.

Case 3. A 7 month old, 11 pound boy, admitted to the hospital because of congenital heart disease. His history was that of repeated respiratory infections, chronic cough and cyanosis accentuated by crying.

Physical examination revealed a grayish-blue cyanosis and slight clubbing of the fingers. There was precordial bulging. A systolic thrill and a grade 3 systolic murmur were maximum at the left sternal border in the third interspace.

The electrocardiogram was normal. Cardiac fluoroscopy and x-ray film of the chest revealed that the heart was enlarged, both to the right and left. The left atrium and the left ventricle were considerably enlarged. The pulmonary arteries pulsated on fluoroscopy.

Angiocardiography was performed at 2:15 p.m. under vinyl ether anesthesia giving 10 ml. of 75 per cent Neo-iopax. There was no immediate untoward reaction. At 3:30 p.m. his color was reasonably good; however, at 5:00 p.m. his respirations were rapid and irregular and oxygen therapy was started. By 6:00 p.m. he was gray and cyanotic, his legs were cold and his temperature had risen to 103 F. At 7:00 p.m. the patient had rales in both sides of the chest with marked tachycardia and tachypnea. In spite of Digoxin and oxygen administration, and tracheal aspiration, the patient expired approximately five hours after angiocardiography.

X-rays films of the chest taken after death suggested acute congestive heart failure. Postmortem examination revealed 100 ml. of fluid in the pleural cavities. There was an atrial septal defect with anomalous pulmonary vein drainage into the right atrium. Right ventricular hypertrophy and slight pulmonary edema were present.

Case 4. This 11 month old, 13 pound girl was referred to the hospital because of occipital meningoencephalocele, Klippel-Feil syndrome and congenital heart disease characterized by cyanosis and a heart murmur. Physical examination revealed generalized cyanosis. A grade 3 systolic murmur and a thrill were present in the second and third left interspace parasternally. The electrocardiogram was normal. The chest roentgenogram revealed gross cardiac enlargement predominantly to the left, with the left hemithorax almost completely obscured by the heart shadow. The pulmonary vascular markings were increased. An episode of congestive failure during hospitalization was successfully treated with digitalis and Mercuhydrin.

An angiocardiogram was done under vinyl ether anesthesia with 10 ml. of 75 per cent Neo-iopax. However, the rate of injection was slow and the angiogram was unsatisfactory. After a delay of 10 days the study was repeated under vinyl ether anesthesia. This time a satisfactory angiocardiogram was obtained at 3:30 p.m. with 10 ml. of 75 per cent Neo-iopax. The films showed an atrial septal defect, but a completely satisfactory diagnosis was not established. At 4:30 p.m. a small amount of emesis was noted. At 6:00 p.m. the temperature was 102.6 F. and the apical cardiac rate was 146. By 8:00 p.m. the fever had increased to 105 F. and marked dyspnea was evident. Oxygen was given without benefit and death occurred 12 hours after the administration of contrast substanec. Permission for postmortem examination was not obtained.

Case 5. A 7 pound, 4 month old boy was admitted for evaluation of cyanotic congenital heart disease. Recurrent attacks of paroxysmal dyspnea with severe cyanosis had required morphine for their relief. On physical examination, the heart was found to be of normal size. There was a systolic precordial murmur. X-ray films revealed decreased pulmonary vascularity and elevation of the cardiac apex. An angiocardiogram was done to confirm the diagnosis of tetralogy of Fallot, since it appeared that the need for surgical intervention was urgent. Seven milliliters of 75 per cent Neo-iopax was given rapidly, intravenously, and this was followed by immediate cessation of respiration and apparently asystole, since no heart beat could be heard for approximately three minutes. Artificial respiration was given.

When the heart began beating again its rate was 40 to 50 per minute. The patient continued to have irregular respiration, periods of apnea and bradycardia. Epinephrine, morphine, Coramine and digitalis were used without success; the baby died 8½ hours after angiocardiography, never having recovered from the initial reaction. Postmortem diagnosis was tetralogy of Fallot. The ductus arteriosus was partially thrombosed.

Discussion

Dotter and Steinberg[7] and Howarth[6] have previously determined the effects of intravenous injection of contrast substance on the peripheral arterial pressure and heart rate in man. Their findings are, in general, the same as those reported here, in that there tends to be a precipitous drop in systemic blood pressure accompanied by marked and apparently compensatory tachycardia. This effect would appear to be largely due to the vasodilating action of these agents.[1] Conclusive comparison of the physiologic properties of these different substances cannot be drawn from this number of observations. The demonstrated physiologic effects of Diodrast would not appear to justify the greater number of deaths reported subsequent to its use compared to those reported after the use of Neo-iopax or Urokon. This, as stated by Dotter and Steinberg,[7] appears to be related to the greater frequency of utilization of Diodrast compared to the other compounds.

An atrial septal defect may be demonstrated angiocardiographically when evaluation by clinical means indicates only a left-to-right shunt. In a series of acyanotic patients with atrial septal defect who underwent cardiac catheterization in this laboratory and in whom the left atrium was catheterized, the left-to-right pressure gradient averaged +1.4 mm. Hg. In 40 per cent of our animal studies, injection of contrast media elevated the right atrial pressure 1.5 mm. Hg or more; even without a decrease in left atrial pressure due to deep inspiration such an elevation might be expected to reverse the usual gradient.

The changes observed in pulmonary artery pressure would not seem to be clinically significant if they are of the same degree in the human subject as they are in the experimental animal. The one fatality in which hemodynami studies were performed during angiocardiog raphy (case 1) revealed marked elevation i pulmonary artery pressure prior to the injec tion of Neo-iopax, and it became much highe after the injection. The response of th pulmonary arterial pressure may be relate to already existing pulmonary vascular damag and to the capacity of the pulmonary arteriole to dilate, so as to permit a viscous substanc to pass through them. In these animal experi ments, pressure increases were more marke in the right atrium and pulmonary artery whe the contrast substance was delivered directl into the pulmonary artery. This presumably i due to the decreased dilution under suc circumstances.

Immediate death after angiocardiography may be related to right-to-left shunts which cause venous blood and contrast substance to enter the systemic vessels and precipitate fatal medullary depression.[7] It would appear that our experimental observations support the shunt portion of this concept. The elevation of right atrial pressure produced by administration of a contrast substance may be sufficient to reverse a left-to-right interatrial shunt. Since the elevation in right atrial pressure may persist for 25 seconds, the reversed shunt might last for a comparable period. By the time the right atrial pressure has returned to normal, the contrast substance has produced a decreased peripheral arterial pressure. This would tend to prolong and increase right-to-left shunting at the ventricular level or from the pulmonary artery to the aorta. In such conditions as tetralogy of Fallot, Eisenmenger's complex, and patent ductus arteriosus or aortic window with pulmonary hypertension, the expected effect of the drop in peripheral arterial pressure might be a hazardous increase of the right-to-left shunt at the expense of the already reduced pulmonary blood flow. A fatal cardiac arrhythmia or central nervous system depression under such circumstances would not be surprising.

Nearly all the angiocardiograms in this series were done with Neo-iopax, and as already noted, 5 deaths occurred with this substance

following 283 angiocardiograms in 249 patients. This experience should be contrasted with 6,24 angiocardiograms collected by Dotter and Steinberg in which 26 deaths occurred,[7] an incidence of 0.4 per cent. Included in this group were over 700 angiocardiographic studies done with Neo-iopax by Dotter and Steinberg without a death.[7] Many of the patients in the present series were critically ill; in this regard other deaths in this hospital not included in the series are of interest. One patient, anesthetized for angiocardiography, died before any contrast substance was given. Another died prior to anesthesia during the exposure of a suitable vein for angiocardiography. Two others developed cerebral thrombosis after the procedure, and subsequently died. It could not be stated unequivocally in either case that the thrombosis was precipitated by the angiocardiographic examination, although the capacity of Neo-iopax to cause thrombosis of vessels is well known.[11]

It is always difficult, with patients as ill as these, to determine the immediate factors precipitating death, but those here reported seem to be clearly related to the angiocardiogram. Only in case 2 was death immediate, and it appears that fatal cardiac arrest must have occurred. Temporary cardiac arrest also occurred in case 5 and probably precipitated the fatal result. In case 1 there was massive infarction of the right lung, possibly due to a specific sensitivity reaction. The other 2 cases had terminal febrile episodes associated with dyspnea and pulmonary congestion suggesting either pulmonary edema from the contrast medium or acute cardiac failure. Failure may result from the degree of pulmonary hypertension that occurred in case 1; however, since the pulmonary artery pressure was not measured in these patients, no causal relationship was established. In addition, petechial hemorrhages in the brain similar to those described by Broman and Olsson[4] may have occurred to explain the hyperpyrexia and pulmonary edema. Dissection of the central nervous system was not performed in these postmortem examinations.

Conclusions

1. Five deaths subsequent to Neo-iopax administration for angiocardiography are reported.

2. Experimental observations in dogs concerning the physiologic effects of several contrast substances on heart rate, and pressure in the right atrium, pulmonary and femoral artery, are described.

3. Each of these contrast substances may produce elevation in right atrial and pulmonary artery pressures followed by systemic hypotension and tachycardia.

4. The effects of these alterations in the presence of abnormal circulation are discussed.

Summario in Interlingua

1. Es reportate cinque mortes post administrationes de Neo-iopax in examines angiocardiographic.

2. Es describite observationes experimental in canes in re le effectos physiologic exercite per varie substantias de contrasto super le velocitate del corde e le pressiones dextero-atrial, pulmono-arterial, e femoro-arterial.

3. Omne iste substantias de contrasto pote producer un elevation del pressiones del atrio dextere e del arteria pulmonar, sequite per hypotension systemic e tachycardia.

4. Es discutite le effectos de iste alterationes in le presentia de un circulation anormal.

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Oscillation-Free Ballistocardiography

A Simple Technic and a Demonstration of Its Validity

By Irwin Hoffman, M.D., Milton Kissin, M.D., and Myron M. Schwarzschild, M.A.

Body motion resulting from cardiac forces may be recorded as displacement, velocity or acceleration by a variety of methods. None of these is identical with the cardiac force curve because of distortion due to body oscillations. Schwarzschild devised an electronic mixer that combines displacement, velocity, and acceleration in any proportion desired. This device permits recording ballistocardiograms that are free of oscillations due to body resonance. Validity of the technic was established by the identity of strain gage records of forces applied to a log phantom with simultaneous records obtained with the method presented.

MUCH current basic research in ballistocardiography is devoted to methods that attempt to eliminate from the records the effects of body oscillations. Rappaport[1] has summarized most of these technics and has introduced one of his own. These methods,[1-3] in general, have in common the elimination or damping of the parasitic body oscillations in some manner by the bed or other apparatus that directly supports the body. The transducer then directly senses the oscillation-free motion, which can be recorded as displacement, velocity or acceleration. Another technic for obtaining "force" curves, which utilizes a conventional pickup, requires for each subject an individually prepared special electronic filter.[4]

Schwarzschild[5] devised an aperiodic system that requires no special ballistocardiographic bed and uses the conventional coil and magnet transducer. This paper reviews Schwarzschild's technic and presents evidence indicating that true force curves are recorded. The method is as follows:

An uncorrected velocity curve is picked up by a Dock-type coil and magnet transducer (from which the condensers have been removed) and is fed into an electronic computer (fig. 1). Here the velocity curve is integrated by one circuit to displacement and differentiated by another to acceleration. A third circuit combines the displacement, velocity, and acceleration in any proportion that the operator may select.

With the sensitivity of the pick-up reduced to 10 per cent of normal, a measured footward force is applied to the shoulders and suddenly released. The effect is the same as the application of a constant headward force of the same magnitude and has the advantage of being easily measured. Naturally, if one were to record the body displacement, velocity or acceleration resulting from this single force, a series of waves would be observed. When the "mixed" circuit is used, however, a combination of displacement, velocity and acceleration can readily be found that results in a single wave, that is, an oscillation-free record (fig. 2).

Once the correct setting of the "mixed" circuit has been established for a given subject, the transducer sensitivity is increased to normal and the ballistocardiogram recorded. The records thus obtained are believed to be free of oscillatory influences, and closely resemble "force" curves obtained by other methods. Figure 3 shows, for a normal subject, displacement, velocity and acceleration records, respectively, compared with the "force" curve as obtained with the Schwarzschild technic.

Direct proof that this technic truly recorded force was sought. For this purpose, a heavy wooden log supported by rubber cushions was used as the phantom. A strain gage was used to measure forces applied to one end of the log, while the transducer was positioned so as to sense motion at the other end. Figure 4 shows the results obtained when the motion of the log was recorded as displacement (*A*), velocity (*B*), or acceleration (*C*). The lower record in each instance is the strain gage measurement of the forces applied. It is readily apparent that the curves are dissimilar. The force curve, sensed by the strain gage, is free of after-oscillations.

From the Departments of Physics and Medicine, Beth Israel Hospital, New York, N. Y.

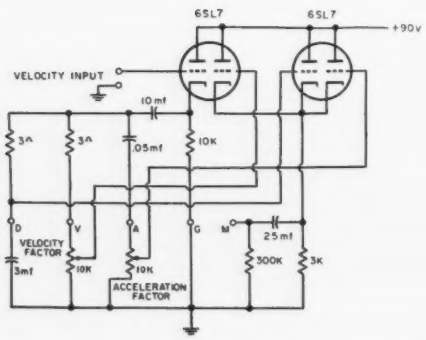

FIG. 1. Circuit of the electronic computing system. The velocity input may be obtained from a velocity transducer directly, if the output of the transducer is high enough. With our pickup (made by Everett M. Hill, Ellsworth, Me., but with condensers removed) additional amplification is necessary, but is not shown on the diagram. The terminals marked *D*, *V* and *A*, when paired with *G*, yield voltages proportional to displacement, velocity and acceleration, respectively. The voltage of terminal *M*, when paired with *G*, is the "mixed" output. The proportion of velocity and acceleration relative to displacement is determined by the settings of the potentiometers marked "velocity factor" and "acceleration factor."

At this point, the Schwarzschild technic was applied to the log phantom and a setting was determined for the "mixed" circuit which eliminated oscillations. Comparison was then made between the strain-gage force record and that obtained with the technic being tested. Figure 5*A* illustrates the determination of the proper setting. The "mixed" circuit curve is above and displacement, below. In figure 5*B* the mixed circuit record (above) was recorded simultaneously with the strain gage record (below) of forces applied to the log phantom. The virtual identity of the two curves is at once obvious.

SUMMARY AND CONCLUSIONS

1. Oscillation-free ballistocardiograms may be obtained with conventional equipment plus a special electronic circuit. Tracings thus obtained closely resemble "force" curves obtained by other technics.

2. Application of this method to a log phantom yielded force curves identical with those obtained by strain-gage measurement of the actual forces applied to the log.

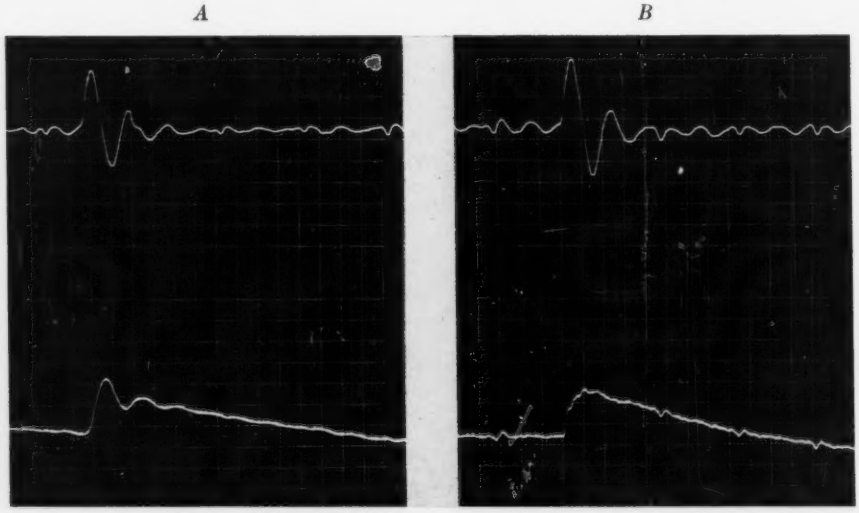

FIG. 2. Adjustment of the "mixed" circuit to yield oscillation-free records from a normal human subject. Transducer sensitivity reduced to 10 per cent of normal, which renders the cardiac ballistic curve vestigial, but still visible. *A*, velocity above, "mixed" circuit below, prior to adjustment. *B*, same, except that changing the proportions of displacement, velocity and acceleration has eliminated oscillations from the "mixed" circuit record. (Condenser coupling in the amplifier causes the slow return to the base line.)

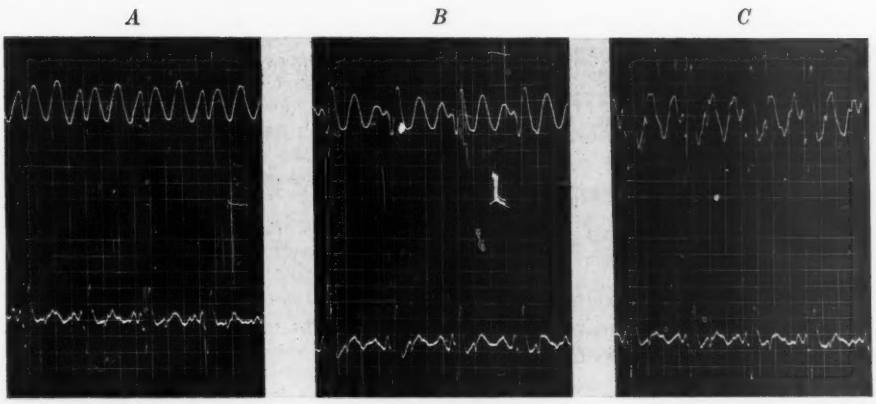

FIG. 3. Comparison of oscillation-free ballistocardiogram of a normal human subject (below) with displacement (*A*), velocity (*B*) and acceleration (*C*) records obtained simultaneously.

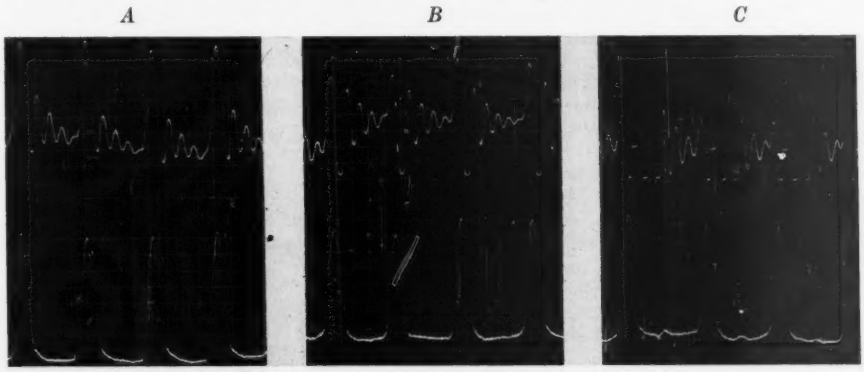

FIG. 4. Records obtained using a heavy log phantom as subject. Below (*A*, *B* and *C*) are strain-gage records of forces applied to one end of the phantom. Above are the displacement (*A*), velocity (*B*) and acceleration (*C*) records of the motion produced at the other end of the log. Note that oscillations are absent from the strain-gage force record.

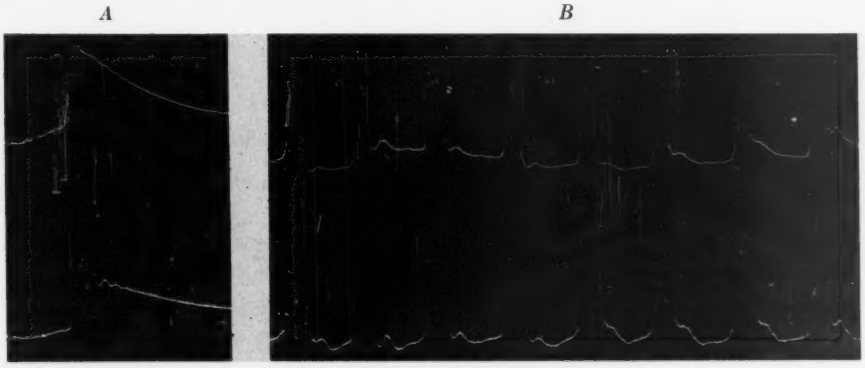

FIG. 5. *A*, adjustment of "mixed" circuit, using the log phantom as subject. Above, tracing resulting from the application of a constant force as recorded by adjusted "mixed" circuit; below, a simultaneous displacement record showing oscillations. *B*, comparison of strain-gage force curve (below) with oscillation-free ballistocardiogram as obtained simultaneously from the log phantom during the application of forces to the log. Note the virtual identity of the curves.

3. The method may be readily adapted for quantitative studies of cardiac forces.

Summario in Interlingua

1. Ballistocardiogrammas sin oscillation es obtenibile per le equipamento conventional supplementate per un circuito electronic special. Registrationes assi obtenite es similissime a curvas de "fortia" obtenite per altere technicas.

2. Le application de iste methodo a un trunco de ligno (serviente como phantasma) resultava in curvas de fortia identic con illos obtenite per le mesuration, per medio de un tensiometro, del fortias realmente exercite super le trunco de ligno.

3. Le methodo es facilemente adaptabile pro studios quantitative de fortias cardiac.

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Posthypothermic Circulatory Failure

I. Physiologic Observations on the Circulation

By Emil Blair, M.D., A. Vernon Montgomery, Ph.D., and Henry Swan, M.D.

Certain aspects of cardiovascular function were studied in dogs that were cooled to 30 C. without ventilatory assistance, and rapidly rewarmed in warm water. While in the hypothermic state, the animals appeared to make an adequate cardiovascular adjustment to the lowered body temperature. Upon rewarming, however, each animal incurred an acute circulatory collapse, which was characterized by a low cardiac output, diminished ventricular work, hypotension, hyperpnea, and increased arteriovenous oxygen difference. It is uncertain whether this circulatory failure is central or peripheral in origin.

FOLLOWING experimental hypothermia in the dog cooled to temperatures as low as 20 C., the animal will return to a normal physiologic state upon rewarming.[1-7] The deaths that did occur were categorized into essentially 3 groups: (1) ventricular fibrillation or cardiac asystole, (2) circulatory collapse, and (3) respiratory collapse.

On the other hand, some animals were not normal physiologically for some time after rewarming even if they survived. Bigelow[3] found a low cardiac output in 1 animal for one hour following rewarming. Reduced cardiac output has also been shown by Prec and co-workers,[9] by Ross,[10] and by Sabiston and associates.[11]

The present report concerns the cardiovascular status of the dog cooled to the moderate level of 30 C. and rapidly rewarmed. It has been found that the animal rapidly rewarmed develops acute circulatory failure, which persists for at least three hours.

Method

Apparently healthy mongrel dogs in the weight range of 12 to 38 Kg. were used. The experiments were done from October 1954, through April 1955. Food and water were withheld for a period of 12 hours prior to the study. No premedication was administered. The animals were anesthetized with chloralose, 100 mg./Kg. The agent was dissolved in boiling saline solution, cooled to body temperature, and kept in a warm bath to prevent crystallization. Under fluoroscopic vision two no. 8 cardiac catheters were introduced into the right heart. One of these was placed into the right or left pulmonary artery and the other into the right atrium. A femoral artery was cannulated with a no. 18 Cournand needle. An endotracheal catheter was made airtight by a ligature around the trachea placed through a small wound in the neck. The animal was heparinized, 3 mg./Kg. A rectal thermometer was inserted into the sigmoid for recording of temperature changes. Lead II of the electrocardiogram was monitored continuously on an oscilloscope. Respirations were unassisted, but were recorded at regular intervals.

Pressures were transmitted to a strain-gage amplifier and recorded on a multichannel oscilloscope-type recorder.* Mean pressures were either electronically integrated or computed with a compensating planimeter. Expired air samples were analyzed by the Scholander method, duplicate samples were accepted if within an error of 0.06 volumes per cent. Blood gas determinations were done by the Van Slyke-Neill method, with duplicate samples falling within a margin of 0.2 volumes per cent. The expired air from the tracheal catheter was collected in Douglas bags, measured in a Tissot spirometer, and corrected for volume at standard conditions (STPD). The pH was determined with a Beckman pH meter with the water bath adjusted to the temperature of the animal. Cardiac output was calculated by the Fick principle, and stroke volume was computed from the output and the rate. From the output and the mean arterial pressure, the total peripheral resistance

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* Manufactured to our specifications by Electronics for Medicine, Inc., White Plains, New York.

(*TPR*) and the work of the left ventricle (*LVW*) were computed as follows:

1. $TPR = \frac{BPm}{Q/T}$ (1332) wherein,

TPR = resistance in dynes seconds/cm.^{5}
BPm = mean pressure in systemic artery in mm. Hg
Q/t = cardiac output in ml./sec.
1332 = conversion factor from mm. Hg to dynes/cm.^{5}

2. $LVW = \frac{(CI \times 1.055)(BPm \times 13.6)}{1000}$ wherein,

LVW = work in Kg. M./min./M^2
CI = cardiac index† in L./min./M.^{2}
1.055 = specific gravity of blood
BPm = mean blood pressure in mm. Hg
13.6 = specific gravity of Hg

Following anesthetization, a period of 30 minutes was allowed in order to reach a steady state before baseline normothermic studies were made. Then the animal's hair was clipped (no depilation was done), and the animal was immersed in a bath of ice water up to its neck. It was removed from the ice bath when the rectal temperature dropped to 32 C. The temperature continued to fall another 2 C. Observations were made again at this time and also an hour later at the same temperature (30 C.). The animal was then placed into a warm bath 42 to 45 C. and rewarmed rapidly. When the rectal temperature returned to 35 C., the animal was removed and dried thoroughly. Studies were made at the end of the rewarming period and again three hours later when the temperature had risen another degree to 36 C.

Blood was replaced, milliliter for milliliter, immediately after withdrawal of samples. The blood was not previously cooled. The amounts of transfusion were so small that they did not noticeably affect the blood gas content or rates of cooling.

During cooling, anesthesia was maintained at a level sufficient to depress shivering because shivering markedly prolongs the process and predisposes the animal to cardiac irregularities, particularly ventricular fibrillation. During the period of cooling, muscle relaxation must be complete to permit rapid induction of the state of hypothermia. Curare or curare-like agents were not employed because artificial or assisted respiration was not used, and partial or complete respiratory arrest in early stages of cooling is undesirable.

During the rewarming period no attempt was made to control shivering, and only enough anesthetic agent was supplied to keep the animal asleep during the technical manipulations of the study. Shivering was not controlled at this time for several reasons: (1) interest was centered on the effect of rapid rewarming and, consequently, the process of shivering, a normal response of the temperature regulating mechanism of the dog, was permitted; (2) the procedure currently used in cooling and rewarming patients was followed; (3) in the dog shivering during rewarming is very active so that its depression would require massive supplemental anesthesia possibly resulting in marked alterations in physiologic chemistry and circulatory dynamics.

A control series of dogs studied under chloralose anesthesia alone revealed none of the cardiovascular changes to be described.

† The cardiac index was derived by dividing the output by the surface area which was calculated from the formula:

$$SA = (\text{log wt. in Kg.})^{2/3}$$

Results

Acceptable data were obtained in 15 animals. Of these, studies were done three hours after warming in 8. Five deaths occurred in the entire group at intervals of 1 to 12 hours after rewarming. All the data are tabulated in table 1.*

Considerable variation was observed from animal to animal and during the periods immediately following a change in temperature; there was much less variation during a steady environmental state. Upon cooling and also on rewarming, there was considerable scatter in the measured values, especially in the A − V O_2 difference and in the *TPR*. There was less variation from one animal to the other upon entering a steady state.

Upon cooling to 30 C., there was a significant decrease in mean femoral artery pressure with little change noted after one hour of a steady state of hypothermia (fig. 1). At the same time, the peripheral resistance also became elevated. The heart rate declined. Upon rewarming, the hypotension persisted although the peripheral resistance remained high. The heart rate returned to normal levels, but did not exceed them, despite the persistent hypotension.

The cardiac index declined considerably upon cooling with no significant change in A − V O_2 difference (fig. 2). No change was noted an hour later. On cooling, the work of the heart (*LVW*) decreased approximately 60 per cent. Upon rewarming, the A − V O_2 difference increased immediately often to

* In comparing any two groups of data in this study, a p value of $< .05$ was accepted as significant

TABLE 1.—*Summary of Data—Cooling to 30 C. and Rewarming*

	Normothermia		Hypothermia						Rewarmed											
	36 C.		30 C.			30 C. 1 hour			35 C.			36 C. 1 hour			36 C. 2 hours			36 C. 3 hours		
	Mean	S.D.	Mean	S.D.	p*	Mean	S.D.	p†	Mean	S.D.	p*	Mean	S.D.	p*	Mean	S.D.	p*	Mean	S.D.	p*
Femoral artery pressure mm. Hg	120	28	92	20	$<.005$	86	21	$>.05$	87	37	$<.02$	98	40	$>.05$	115	37	$>.05$	94	31	$<.02$
Right atrial pressure mm. Hg	2	2	0.5	1.9	$>.05$	0.5	2	$>.05$	2	7	$>.05$	$-.05$	2	$>.05$	-0.5	1.7	$>.05$	-0.5	1.9	$>.05$
Heart rate per minute	140	40	98	35	$<.005$	88	38	$>.05$	137	43	$>.05$	160	35	$>.05$	158	44	$>.05$	161	39	$>.05$
A-V O_2 difference vol. %	4.30	1.30	4.90	2.20	$>.05$	5.30	1.40	$>.05$	9.20	3.00	$<.005$							9.20	1.40	$<.005$
Cardiac index L/min./M^2	4.26	0.80	1.62	0.57	$<.005$	1.45	0.38	$>.05$	2.15	1.46	$<.005$							2.67	1.76	$<.005$
Left ventricular work Kg.M./min./M.^{2}	7.76	1.87	2.31	0.87	$<.005$	1.85	0.53	$<.005$	3.33	3.10	$<.005$							4.26	3.82	$<.02$
Minute ventilation L./min./M^2	4.64	1.48	1.56	0.65	$<.005$	1.75	0.83	$>.05$	6.48	2.53	$<.02$							7.56	2.26	$<.02$
Oxygen consumption ml./min./M^2	161	23	70	20	$<.005$	71	19	$>.05$	170	113	$>.05$							216	106	$>.05$
Total peripheral resistance dynes cm.^{5}/M^2	2600	700	5900	3000	$<.005$	6100	3300	$>.05$	5200	2900	$<.005$							4400	2700	$<.02$

* Compared with normothermia

† Compared with initial hypothermia

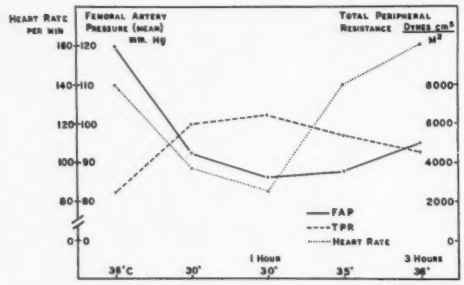

FIG. 1. Vascular physiologic effects during hypothermia and rewarming (mean values). The arterial pressure and the peripheral resistance fail to return to normal on rewarming.

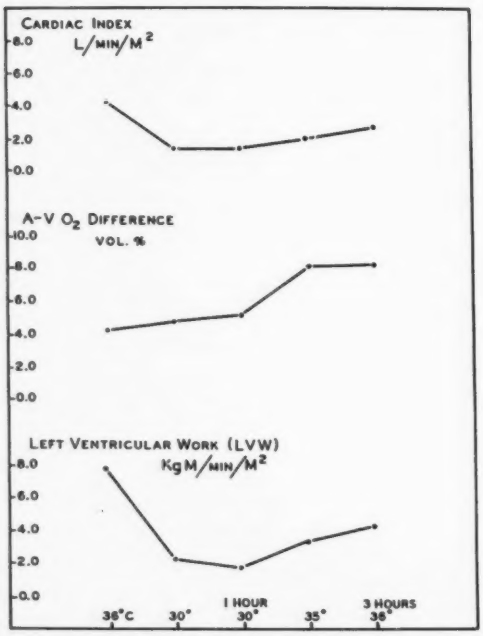

FIG. 2. Cardiac index, atriovenous oxygen difference, and left ventricular work during hypothermia and rewarming. On rewarming the cardiac index is low, the arteriovenous oxygen difference increases, and the left ventricular work is below normal.

greater than normal figure, with a persistent low cardiac index. At this time, the *LVW* increased, but not to normal. Three hours after rewarming the A − V O_2 difference continued to increase, with a continued low cardiac index and decreased *LVW*. In short, no significant

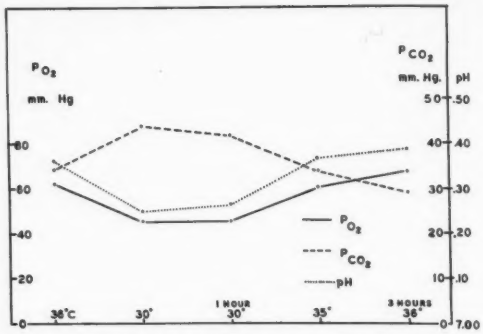

FIG. 3. Arterial blood gas changes during hypothermia and rewarming (mean values). Significant acidosis develops on cooling, with fall in oxygen tension and increase carbon dioxide tension during hypothermia. On rewarming there is a return to normal.

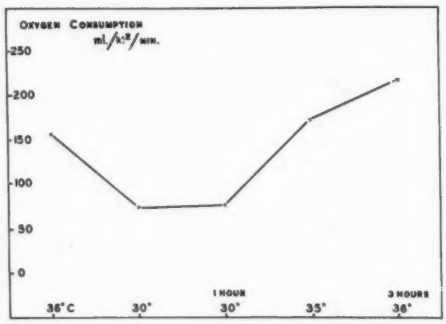

FIG. 4. Oxygen consumption during hypothermia and rewarming (mean values). During hypothermia there is a marked decrease in oxygen consumption and a significant increase above normal on rewarming.

improvement occurred in the circulation during the three hours following rewarming.

As might be expected with unassisted respiration, respiratory acidosis developed, but it disappeared on rewarming (fig. 3).

The total oxygen consumption decreased about 50 per cent on cooling to 30 C. (fig. 4). One hour later there was no significant change. Upon rewarming, however, the consumption rose to levels above control and three hours later was even greater.

Figure 5 illustrates these characteristic changes in one animal. In some animals the changes were less extreme and the return to normal on rewarming was more pronounced; in others, the changes were greater and the animals succumbed.

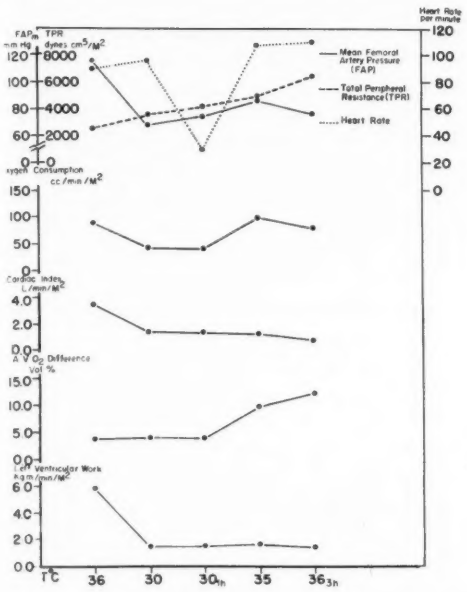

FIG. 5. Physiologic changes during hypothermia and on rewarming in a typical experiment (animal protocol #54-107). Three hours after rewarming the animal is in circulatory failure.

A linear correlation was found between total oxygen consumption and cardiac output in normal, hypothermic, and rewarmed animals (fig. 6). Both variables decreased proportionately in the cold state, indicating that circulation was adequate for the oxygen demand. As seen in figure 7, however, in the rewarmed animal the output rose relatively less than oxygen consumption. The circulation was therefore inadequate for the oxygen demand.

DISCUSSION

A major physiologic effect of cooling is lowered body metabolism.[5, 12] In consequence ventilation is reduced, as is cardiac activity (manifest by slow heart rate, low cardiac index, reduced ventricular work, and lower blood pressure) with subsequent decrease in blood flow in both the greater and lesser circuits. With some exceptions,[9, 11] investigators generally observed that animals tolerated cooling and rewarming well and returned to normal in all respects upon rewarming.

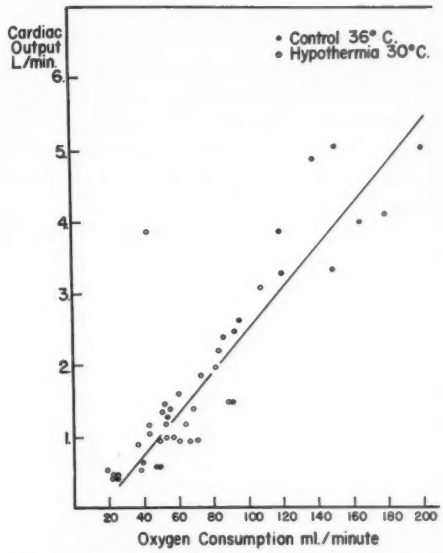

FIG. 6. Relation between cardiac output and oxygen consumption during cooling. The linear relationship both during control normothermia and hypothermia is demonstrated. There is actually a wider scattering during normothermia than during the cooled state. In both stages the circulation is adequate.

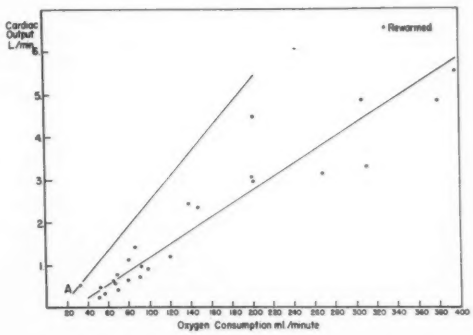

FIG. 7. Relation between cardiac output and oxygen consumption during rewarming. The rewarmed animals all fall well below line A derived in figure 6. The circulation is inadequate.

Data from the present study concerning hypothermia at 30 C. of one hour's duration, corroborated part of this view: that the animal adjusts adequately to a state of hypothermia. Upon rapid rewarming, however, a striking abnormality, which can be described as circu-

latory failure, persisting for at least 3 hours, was observed consistently in every animal.

Upon rewarming to normothermia, the animal became hyperpneic and oxygen consumption increased. During this period of time shivering was active. The blood pressure, which fell during hypothermia, failed to rise, although the heart rate returned to the control level. Clinical signs of circulatory collapse appeared, indicated by a pale dry tongue and overbreathing. The A $-$ V O_2 difference widened markedly and there was a low cardiac index, decreased left ventricular work, and persistently elevated resistance to blood flow. At this time, the circulation was not adequate; survival depended on maximal extraction of oxygen from the hemoglobin. We believe this phenomenon results from serious decrease in effective circulating blood volume or myocardial failure.

During the cooled state, it seems probable that blood is shunted into reservoirs and the reduced cardiac output is adequate during the hypothermic state. Upon rewarming the cardiac output and blood flow do not return to normal, but a state of circulatory shock develops, with continued low output. The mechanisms involved in reduction of effective circulating blood volume may be a failure of homeostatic mechanisms to release blood from reservoirs into the effective circulation and an overexpansion of the capillary bed with a peripheral trapping of blood. Despite the severe degree of hypotension, tachycardia that is ordinarily seen in states of low volume circulatory collapse was absent. The state of the heart during hypothermia should be reviewed before consideration of possible myocardial dysfunction in the rewarmed state. Anoxia of the heart during hypothermia has been reported with resultant circulatory collapse.[6, 17] Adequate myocardial oxygenation has been indicated, however, by other investigators[12, 18] and ourselves[20] in finding no change in the A $-$ V O_2 of the myocardium. Our observations confirm the latter view.[20] Furthermore, even with unassisted ventilation, there was adequate oxygenation at the temperature level studied. There appears to be no myocardial inadequacy during hypothermia.

It has previously been demonstrated that in acidosis the myocardium enters a positive K+ balance.[19] According to Szent-Györgyi,[21] this positive balance leads to a decrease in the tension developed during ventricular contraction. The net result of these myocardial metabolic derangements would be a reduced ventricular efficiency, manifest by a lowered ability to work and a consequent low output. This sequence has not yet been definitely established, however. The oxygenation and potassium balance of the myocardium at this stage of the posthypothermic state will be the subject of a subsequent report.[20]

The normal right atrial pressure in the rewarmed animal is inconsistent with myocardial insufficiency; with prolonged reduction of cardiac output the venous return should become overpowering if the effective circulating blood volume has been restored. Furthermore, pulmonary hypertension, which is a frequent accompaniment of acute myocardial failure, was absent in the present study.[22]

It is possible, of course, that even in the absence of direct myocardial muscular derangements during rewarming, the circulatory collapse might affect the myocardium secondarily with the same net results.

The nature of this posthypothermic circulatory failure is unclear at present. The problem is of great importance, however, for the proper understanding and management of general hypothermia. Further studies are in progress in this laboratory.

Summary and Conclusions

Dogs under chloralose anesthesia with unassisted respiration were subjected to a rectal temperature of 30 C. for one hour and rewarmed rapidly.

In the hypothermic state the cardiovascular system in the majority of the animals appeared to adjust adequately to the change in environment for the period observed.

Upon rewarming, every animal developed acute circulatory collapse, characterized by low cardiac output, diminished ventricular work, hypotension, hyperpnea, increased A $-$ V O_2 difference, and increased total oxygen consumption.

The exact mechanisms for the circulatory

f ilure are not known, although it is suggested t ıey may involve diminished effective circulat- i g blood volume or myocardial insufficiency (both.

ACKNOWLEDGMENT

The authors wish to acknowledge the constructive (iticism afforded by Dr. Clarence A. Maaske in the] reparation of this manuscript. The competent labo- ı itory analyses were done by Mary L. Willcox, Vir- ; inia Beresford, and Shirley Gates.

SUMMARIO IN INTERLINGUA

Canes sub anesthesia a chloralosa sin assis- tentia respiratori esseva subjicite durante un hora a un temperatura rectal de 30 C e recale- facite rapidemente.

In le stato hypothermic le systema cardio- vascular del majoritate del animales pareva adjustar se adequatemente al ambiente alterate durante le periodo del observation.

Post recalefaction, omne le animales dis- veloppava un acute collapso circulatori, char- acterisate per basse rendimentos cardiac, reducite labor ventricular, hypotension, hyper- pnea, augmentate differentia atrio-ventricular de O_2, e augmentate consumption total de oxygeno.

Le exacte mechanismos del disfallimento circulatori non es cognoscite, sed nos postula le possibilitate que illos involve un reducite effective volumine de sanguine circulante o insufficientia myocardial o ambe iste factores.

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CLINICAL PROGRESS

Current Research and Problems of the Coronary Circulation

By DONALD E. GREGG, PH.D., M.D., AND DAVID C. SABISTON, JR., M.D.

HEART disease, especially coronary artery disease, continues to be one of the foremost problems in medicine today. A good estimate is that about one third of those who die from heart disease in the United States do so from a primary coronary insufficiency related to atherosclerosis as the dominant factor, one third die from primary coronary insufficiency associated with cardiac hypertrophy and increased cardiac work arising from valvular lesions and increased blood pressure, and one third as a result of a primary myocardial insufficiency.

Of the available methods of study, none gives detailed or accurate information regarding the coronary system in the normal or diseased staet. Such studies require precise methodology that is difficult to apply to the heart because of its gross inaccessibility. For this reason various types of instrumentation are introduced in order to obtain hemodynamic and metabolic data, but such data are often of doubtful value. Accordingly, advances in the field of the coronary circulation are based on a combination of difficult precision instrumentation applied directly to the exposed or isolated heart and of questionable indirect methodology applied to the heart in the intact state. By synthesis of available experimental facts, however, considerable progress has been made toward the solution of certain problems in this field.

Metabolic Patterns in the Heart. Since the ability of the heart to do work depends basically on its biochemical activity leading to muscular contraction, any definitive analysis of the phenomena of heart failure or coronary insufficiency is dependent upon an understanding of the normal metabolism of cardiac muscle. Basic chemical patterns in cardiac muscle have been found similar to those in other muscles and tissues. The catabolism of fat, carbohydrate, and protein produces free energy, about half of which is dissipated as heat and half is captured as phosphate bond energy. The latter is used for muscle cell work and for various anabolic activities such as synthesis of glycogen, lipids, proteins, and enzymes. These catabolic and anabolic reactions proceed simultaneously under the influence of a complex system of enzymes, coenzymes (from the vitamin B complex), and hormones. Compounds such as adenylic acid and creatine accept the high energy phosphate moieties from the oxidation of substrate to form phosphocreatine and adenosine triphosphate. It is believed that the ultimate contractile unit in muscle tissue is the actomyosin fibril, a conjugate of two muscle proteins, polymerized actin and myosin. Conversion of actin into polymerized actin requires energy that is transferred from nucleotides such as adenosine triphosphate and is released enzymatically, presumably during ventricular diastolic relaxation, so that shortening of the muscle fibril can take place during the next systole. Up to the present time biochemists have appeared to be interested primarily in adenosine triphosphate as the chief nucleotide furnishing the energy for contraction. However, recent work in at least two laboratories has shown that the content of adenosine triphosphate and adenosine diphosphate is the same in the resting and the beating heart.[1, 2] This raises the question of whether or not adenosine triphosphate is the

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main donor of phosphate bond energy and indicates that a new revolution in the physiology of muscular contraction may have begun.

Coronary catheterization studies in dog and man have indicated that the heart can choose its fuel from a variety of foodstuffs.[3] Thus, it is largely independent of fluctuations in its chemical environment. To determine the quantitative contribution of fat, carbohydrate, and protein to the energy production of the heart, i.e., its oxygen consumption, measurements have been made of their cardiac extraction (coronary artery − coronary sinus difference), their total uptake [coronary flow × (coronary artery − coronary sinus difference of substance)], and the myocardial respiratory quotient (coronary sinus − arterial carbon dioxide difference)/(coronary artery − coronary sinus oxygen difference). In general, the myocardium of the normal left atrium and ventricle has been found to extract oxygen, glucose, lactic and pyruvic acids, fatty acids, ketone bodies, and amino acids in direct relation to the arterial level of each substance. Excellent correlation has been demonstrated between the myocardial respiratory quotient and the myocardial uptake of a substance. During fasting, the heart can derive its energy from fat as indicated by a myocardial respiratory quotient of 0.7 with a very low extraction and uptake of carbohydrate. In the normal postprandial state, the metabolism of the heart may be based largely on carbohydrate, since its respiratory quotient approximates 0.9, with a high extraction and uptake of carbohydrate and with a negligible uptake of amino acids. Even the substitution of 5 to 10 per cent oxygen for the normal 21 per cent in the inspired air does little to change carbohydrate uptake by the normal heart.

In addition to these patterns of myocardial metabolism in the normal heart, other metabolic changes have been reported in some pathologic and diseased states. Patients with heart failure and decreased cardiac work due to valvular disease show an increased carbohydrate uptake by the heart with a normal extraction of lactate and pyruvate and an increased glucose extraction. The heart in the patient with even mild diabetes appears to

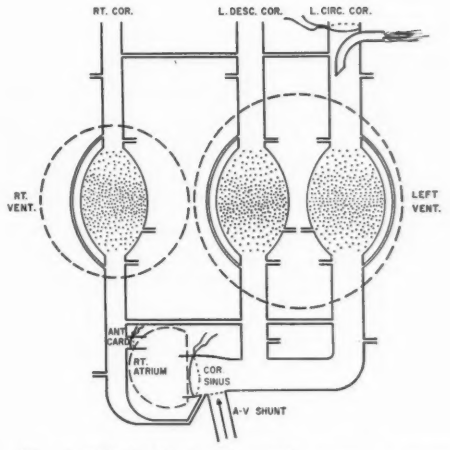

FIG. 1. Schematic drawing of the coronary system.

derive most of its energy from fat, with a post-absorptive respiratory quotient of about 0.7, an increased uptake of fatty acids, and a decreased carbohydrate uptake. It is well to defer detailed consideration of much additional metabolic data that have been reported in other states, because an interpretation must be based on the assumption that oxidation of foodstuffs to carbon dioxide and water is the sole factor in the determination of the myocardial respiratory quotient and of the myocardial extraction and uptake of these compounds including oxygen. Without doubt, storage or conversion into other compounds is occurring concurrently and these activities are especially prominent during changing levels of cardiac activity or of blood substrate.

Basic Regulation and Concepts of Coronary Circulation. In any consideration of the problems of the coronary circulation, certain basic concepts are essential.[4] Beginning with Harvey in the seventeenth century, the anatomic and dynamic details of this system have been elucidated gradually (fig. 1). As in any other vascular system, each of the two coronary arteries that arise from the aorta connects with its capillary bed, its superficial myocardial venous bed, and eventually with the right atrium. The epicardial branches of the coronary arteries and coronary veins also anastomose with each other and with extracardiac arteries and veins. There are numerous

arteriovenous shunts. In addition to these pathways, the arterioles as well as the capillaries and superficial veins connect directly with both ventricular cavities by discrete, deep drainage channels, the arterioluminal, the arteriosinusoidal, and the Thebesian vessels. Despite the presence of these deep channels and the existence of a favorable pressure gradient during systole, they are not used. Balance studies of coronary inflow and outflow have shown that approximately three fourths of the blood entering the left coronary artery drains into the coronary sinus. The remainder of left coronary artery inflow is recovered in the superficial (anterior cardiac) veins of the right myocardium that drain into the right atrium. Most of the right coronary artery inflow appears in these anterior cardiac veins and the remainder (10 to 20 per cent) drains into the coronary sinus. It is presumed that a similar pattern occurs in man.

Consideration of the mechanisms that control the oxygen supply to the myocardium involve certain difficulties not encountered in similar investigations in other organs of the body. The myocardial wall of the left ventricle not only furnishes the pressure head for driving blood into the coronary arteries but also may either offer phasic resistance to coronary flow or actually aid flow by its muscular contraction around the coronary vascular bed. Similarly, the right ventricle rapidly changes resistance to right coronary flow at the same time that left ventricular contraction presents blood to it under a pulsatile head of pressure. However, flow in either coronary artery will vary directly with the effective perfusion pressure head (aortic or central coronary pressure — right atrial pressure) and with the size or mean bore of the coronary bed. The bore of the coronary bed is regulated to increase flow by changes in the intrinsic smooth muscle of the coronary vessels as mediated by nervous, humoral, and metabolic influences ("active coronary dilatation") and by a passive or mechanical mechanism arising from myocardial contraction during systole ("passive dilatation").

Changes in the coronary circulation with acute or chronic alterations in stress make more economical use of the available oxygen and increase the available oxygen supply [coronary flow × (artery − coronary sinus oxygen difference)]. First the biochemical and mechanical processes of the heart muscle adjust, so that a given myocardial oxygen usage results in greater external cardiac work. Second, the coronary vascular resistance decreases and coronary sinus extraction of oxygen increases. In this consideration, it is assumed that all coronary sinus blood has passed through a capillary bed. There are certain problems in the field of effective supply of oxygen, the solution of which has a practical application. Actually, considerable progress has been made in this direction.

The first problem is the identification of the direction and magnitude of the determinants of coronary flow that reside in the myocardial wall, i.e., the quantitative separation of the influence on coronary flow of the intravascular factors from mechanical effects of ventricular systole. This fractionation is of extreme importance, since under normal conditions the only other major factor affecting coronary flow is central coronary pressure, which ordinarily does not change greatly with exercise. Previous attempts to estimate separately the effects of vasomotor action and of myocardial contraction have been based on analysis of phasic flow curves in a coronary artery or vein. Such an indirect approach has led to the opposite conclusions that ventricular systole aids coronary flow and that it tends to throttle coronary flow. These deductions suffer from the assumption that the measured rate of flow in an epicardial artery and vein at the indicated time interval represents actual flow through the myocardium.

Recently, we have applied a technic in our laboratory that is thought to quantitate separately the effect on left coronary flow of the coronary vasomotor state and of ventricular contraction. In the open-chest dog the left coronary artery is perfused from a reservoir of blood at a constant pressure and the coronary flow quantitated by a rotameter, while flow in the coronary sinus is measured by a second rotameter as its blood passes to the right atrium through an indwelling polyvinyl cathe-

t r. Following coronary flow measurements in t e beating heart, the flows are measured d ring prolonged diastolic relaxation induced b peripheral vagal stimulation to remove the r echanical effects of ventricular contraction. The results (of which, figure 2 is typical) have i dicated that coronary flow increases in- v riably during asystole in both the left c ronary artery (13–77 per cent) and in the c ronary sinus (17–76 per cent). The same d rectional trends were observed in similar e periments with electric induction of ven- t icular fibrillation. These experiments have c nvinced us that ventricular contraction (myocardial action during systole) acts to impede coronary flow through the left ventricular wall; the extent of increased flow during asystole represents quantitatively the magnitude of the mechanical or passive factors limiting coronary flow; the new flow level represents that state of coronary dilatation related to the state of the intrinsic smooth muscle in the coronary vessels.

A second basic problem is the estimation of the amount of oxygen used by a ventricle when it is doing no external work. This measurement is vital to the determination of the economy of oxygen consumption by the ventricle, i.e., the mechanical efficiency of its operation, since as in any other muscle its efficiency is estimated by dividing its external work by the difference between its oxygen consumption during the beating state and during its relaxation. In the past, except for the oxygen usage of the relaxed or "resting" heart, these values have been available and many calculations made of cardiac efficiency in normal and pathologic states. Whether such values give even an indication of directional change for efficiency depends upon the magnitude of the unmeasured parameter. It occurred to us that the asystolic heart with its perfused coronary arteries might supply the physiologic situation in which the metabolism of the left ventricle during relaxation could be measured. Accordingly, the experimental preparation and procedures similar to those just described for indicating changes in coronary flow in asystole were used with the addition that the coronary arteriovenous oxygen difference was recorded con-

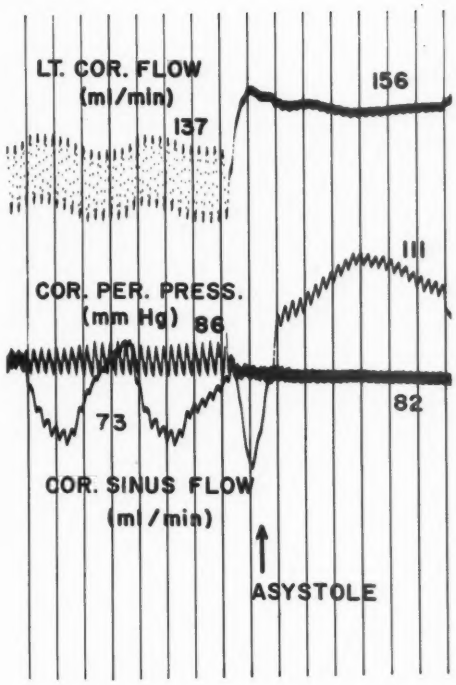

FIG. 2. Reproduction of a record illustrating left coronary arterial inflow and coronary sinus drainage in asystole. The flows in the beating heart are 137 and 73 ml./min. for the left coronary artery and coronary sinus, respectively. With the induction of asystole by vagal stimulation (while perfusion pressure is held essentially constant), arterial inflow rises to 150 ml./min. and coronary sinus drainage to 111 ml./min. The time lines are one second apart.

tinuously by withdrawal of arterial blood and coronary sinus blood through a recording densitometer in the beating and then in the asystolic heart. Thus far, in a number of experiments some of the values obtained for the oxygen consumption of the asystolic left ventricle representing a period when no external cardiac work is performed may be up to half of those in the beating heart. Further experimentation is needed to determine the lowest value obtainable for "resting" oxygen usage of the heart. However, if values of this magnitude for oxygen usage in the resting heart are subtracted from the oxygen value in the beating heart, it is apparent that the value for cardiac efficiency is altered greatly. For this reason no reference will be made to the values

obtained for myocardial efficiency and their significance in a variety of clinical states until their fundamental adequacy can be ascertained.

A second interesting feature of these studies is that coronary sinus oxygen saturation does not begin to rise concomitantly with asystole but rather there is a lag of 10 to 15 seconds after which oxygen saturation rises to a new plateau in 25 to 30 seconds. This indicates that considerable oxygen is consumed by the left ventricle over and above the resting oxygen level from the onset of asystole to the apparent new equilibrium at 25 to 30 seconds. Presumably, this oxygen is used by the myocardium for performance of its work after the work period has been terminated, i.e., the left ventricle contracts an "oxygen debt." This behavior of the coronary flow and oxygen usage of the myocardium during asystole is similar to that observed many years ago by Kramer[5] for skeletal muscle as it went from a condition of rhythmic contraction to the resting state.

Consideration of the State of Performance of the Heart. Probably the most difficult and certainly the most controversial field in cardiology is the estimation of the state of performance of the heart.[6] This consideration is particularly germane here, since depression of myocardial function or heart failure is undoubtedly most often the result of an inadequate coronary circulation even in the absence of mechanical obstruction to the coronary artery.

In seeking a method for determination of cardiac contractility or for evaluation of the dynamic state of the heart, the search for a correlative measurement of stroke work has led in various directions. Upon the basis of findings in the isolated heart, heart-lung preparation, and the open-chest dog in which cardiac size and cardiac work have been increased progressively by large and rapid blood infusions, the basic concept has been formulated that the energy of cardiac contraction (cardiac work) is a function of the extent to which myocardial fibers are stretched during the preceding diastole (diastolic volume). Since tension in a myocardial wall is related to the product of the pressure and radius in its ventricular cavity, curves of the relationship of ventricular end-diastolic pressure (or mean atrial pressure) to stroke work of the respective ventricle have been obtained also in these preparations. Recent expansion of the latter approach in the open-chest dog has indicated that each significant alteration of the circulatory state results in a new curve of relation of atrial pressure to stroke work. As evidenced by such left "ventricular function" curves the state of performance of the left ventricle is improved by mechanical increase in aortic resistance and by epinephrine injection, while severe anemia depresses ventricular function and unilateral depression of left ventricular function is related quantitatively to coronary insufficiency caused by constriction of the coronary artery. The validity of such curves is unquestioned as is their applicability to such preparations provided heart rate and the functional state of the myocardium are unchanged. This experimental approach serves as a useful laboratory method in differentiating between the normal and the depressed or failing ventricle. Without doubt, this relationship of either diastolic size or end-diastolic pressure to cardiac response is a fundamental property of the myocardium as it is in skeletal muscle. However, because of technical and other difficulties, neither of these measurements and comparisons has ever been made in the intact dog or man.

In the normal state, the stimulus to increased cardiac work is generally a combination of exercise and excitement which operates through neural and humoral mechanisms to change quickly and greatly the heart rate, size of great veins and atrial compartments, peripheral resistance, cardiac output, ventricular end-diastolic pressure, and cardiac size. While the crucial experiment admittedly has not yet been done, still there is no correlation in exercise between left ventricular end-diastolic pressure and stroke work; and left ventricular diameter (as determined by an intraventricular gage) and the ventricular diastolic volume (as estimated by x-ray) respond to the stress of exercise by becoming smaller rather than larger in diastole, irrespective of heart rate changes. These observations raise the question of the

elevance of the findings in the abnormal reparation to the problem of the regulation of ie state of performance in the normal ambutory animal or human being. Further advance i this field will depend upon adequate instruental development for the determination of hasic changes in diastolic and systolic venicular volumes in the normal state.

By the use of different approaches, certain ata on basic flow have been established conerning utilization of the left coronary system f man and the dog. Left coronary inflow pproximates 70 ml./100 Gm. of left ventricle er minute; coronary arteriovenous oxygen ifference 10 to 12 ml./100 ml. of blood; left entricular work 3.0 Kg.M./100 Gm. of left entricle per minute. In the heart undergoing eavy stress, values approximating 12 Kg.M./ 00 Gm. of left ventricle per minute for maximum cardiac work are probably a reasonably accurate approximation. These figures were obtained in our laboratory during massive blood infusions in the normal dog and in the dog with a peripheral or aorta-caval fistula, and in man native to sea level or to a three mile altitude and exercising on a treadmill to near exhaustion. Correct values for left coronary flow and myocardial oxygen consumption during natural maximal stress, such as exercise, are not available because of technical difficulties of instrumentation and application.

The extent to which increased oxygen extraction contributes to the available myocardial oxygen supply during increased stress is also undecided because of insufficient study. In some instances, such as an acute increase in systemic blood pressure through mechanical aortic constriction or a blood transfusion, the oxygen level of the coronary sinus is not sigificantly altered despite a considerable increase in systemic blood pressure, left coronary flow, left ventricular work, and oxygen usage. In the presence of acute pulmonic stenosis or aortic stenosis (central to the coronary ostia), in which the central coronary pressure is not elevated, the left coronary flow rises but oxygen content of the coronary sinus drops considerably, and most of the remaining oxygen is extracted. If the stenosis is severe enough there will continue to be an increased coronary flow and extraction of oxygen from the coronary circulation even if, prior to the induced stenosis, the control left coronary inflow is increased 2 to 3 times by raising the central coronary pressure to a very high level. In the heart failing acutely or chronically, oxygen saturation of the coronary sinus is invariably decreased. On the other hand, it is easy to increase considerably the oxygen content of the coronary sinus by injecting certain drugs such as epinephrine and norepinephrine intravenously or directly into the coronary artery. The increase in oxygen saturation of the coronary sinus is generally, although not necessarily, associated with an augmentation of the coronary inflow which supplies oxygen to the needy myocardium in excess of its metabolic demands.

It is exceedingly important to know the level of the oxygen content of the coronary sinus or coronary arteriovenous oxygen difference. Although extraction of this small volume of oxygen cannot increase greatly the myocardial oxygen supply, knowledge of its level enables an estimation of the balance between dilatation arising as the result of increased metabolic requirements in the heart and dilatation from the effects of substances on the smooth muscle of the coronary vessels and on the extent of extravascular compression. If the substance that causes dilatation and increased coronary flow operates mainly through the latter mechanisms, then it will be identified by the fact that as coronary flow increases, oxygen content of the coronary sinus blood increases and the coronary arteriovenous oxygen difference decreases. This might be termed "benign dilatation" and is obviously an excellent situation for the heart, in that it obtains its blood flow cheaply. If, on the other hand, the increase in oxygen supplied to the myocardium by the coronary circuit during stress is less than the increased volume of oxygen used by the myocardial cells, the arteriovenous oxygen difference of the coronary increases. This operation is relatively expensive to the heart and might be called "malignant dilatation." This type of analysis is now being applied to various physiologic states and should

be helpful in the evaluation of the fundamental action of drugs.

Although we cannot as yet weigh the relative role played by these factors in promoting the oxygen supply to the heart in normal stress, such as exercise, there are certain general patterns of hemodynamic responses of the normal heart and of the pathologic nonfailing heart under increased and decreased stress that merit some consideration.[7] In acute hypertension, coarctation of the aorta, increased venous return (whole blood infusion), acute and chronic anoxia, acute and chronic anemia, a chronic peripheral arteriovenous fistula, thyrotoxicosis, and intravenous injection of epinephrine or norepinephrine, there is an increase in the cardiac output, cardiac work, and cardiac oxygen usage. Concurrently, the inflow of the left coronary increases while its vascular resistance decreases. Fractionation of the coronary flow increase between active vasomotor change and passive change in the coronary bed has been attempted only in the situation of an acute elevation of aortic blood pressure and in the case of hypoxia. In the first instance, most of the coronary flow increase arises from an increase in central coronary pressure and active coronary dilatation; in the second case, reduction of myocardial compression and relaxation of smooth muscle in the coronary vessels appear to be equally potent in promoting coronary flow. An exception to this general picture of coronary compensation to increased stress is that of chronic hypertension, in which cardiac output, oxygen consumption, and left coronary flow are unaltered while coronary resistance to flow increases. This deviation is explainable if it is assumed that such hearts with known coronary artery disease have an increased amount of perfused nonmuscle tissue. A second exception is the failing rheumatic, arteriosclerotic, and hypertensive heart, or the acutely failing heart in the heart-lung preparation. These are characterized by a reduction in the output and work of the heart and a normal or mildly increased left coronary flow, while oxygen usage of the left atrium and left ventricle is normal in chronic failure and increased in acute failure. These hearts appear to have lost in part their ability to convert aerobic energy into cardiac work. This deviation is based presumably on the fact that in these hearts that are hypertrophied there are fewer capillaries per unit of myocardium to carry the oxygen and coronary flow.

Interest has been increasing in situations of decreased cardiac stress such as hemorrhagic hypotension and hypothermia.[8, 9] In these states, cardiac output, cardiac work, and cardiac oxygen usage decrease, as does the left coronary inflow. As compared with other vascular beds, the heart appears to be relatively protected, since the ratio of coronary flow to cardiac output is increased considerably. The intracardiac factors determining coronary flow here have not been quantitated separately. Although many oxygen values have been taken from the coronary sinus, the results are too erratic to warrant interpretation.

It has been indicated by some investigators that in sustained hemorrhagic hypotension and in hypothermia, despite the relative maintenance of coronary flow, myocardial depression and failure are present, as evidenced by a rising atrial pressure and cardiac dilatation.[10] Since these parameters can be reversed by increased left coronary inflow without change in blood pressure or blood volume or by intracoronary injection of a sympathomimetic amine (Aramine), this failure is believed consequent upon an insufficient coronary flow. Although one does not question the responses noted, it must be borne in mind that the various surgical insults incident to such an experiment, in addition to the hemorrhage, can in themselves place the heart in failure. Actually, in neither of these situations have we ever observed a rising atrial pressure.

Blood transfusion for the restoration of a normal hemodynamic state often presents a desperate therapeutic problem. In hypotension produced by acute, severe blood loss, it is necessary to restore an adequate circulation to vital areas such as the brain and myocardium as rapidly as possible. The possibility exists that intra-arterial and intravenous transfusion could have quite different hemodynamic effects. The preferential use of the intra-arterial route in acute severe hemorrhagic shock has been

p oposed on the assumption that intra-arterial t nsfusion would produce a more rapid i rease in systemic pressure as a result of a h draulic effect, so that perfusion of the c ronary bed would be more quickly and e ectively re-established, thus favoring the i provement of myocardial function. Some also f el that a larger volume of blood could be t nsfused by the intra-arterial route without p oducing dangerous elevations of venous blood p essure and right ventricular dilatation. How- e er, the experimental studies on the effects of c mparable blood infusions alternately by the a terial and venous routes in the same dog do n t substantiate this view. In our laboratory[8] a d elsewhere, the intra-arterial route did not e evate left coronary flow or arterial pressure e ther more rapidly or more effectively than the intravenous route. Similarly, the route of infusion did not change the effect on either right or left atrial pressures or pulmonary arterial pressure, and excessive elevation of right ventricular end-diastolic pressure (cardiac dilatation) did not occur. These findings were observed in the dog with acute hemorrhagic hypotension, in the dog with prolonged hemorrhagic hypotension, and in the dog at the point of death. It must be borne in mind that the equal effectiveness of the two routes of transfusion does not indicate whether the coronary circulation is insufficient during severe oligemic shock.

Observations in ventricular fibrillation demonstrate an extreme and sustained myocardial resistance to death or to irreversible processes over a long period of time.[11] During fibrillation without coronary perfusion at body temperature fibrillatory motion eventually ceases and cardiac adenosine triphosphate and glycogen levels become minimal; but if coronary perfusion is re-established one hour or more later, within a few minutes strong fibrillatory action returns, as does the resynthesis of high energy phosphate. The heart now uses about half the oxygen as the beating heart and a normal rhythm can be established by countershock. It is of particular interest that dogs will survive after hours of ventricular fibrillation in controlled deep hypothermia in which use of myocardial oxygen is greatly decreased and with only an intermittent and very low level of coronary perfusion. These observations suggest that prolonged ventricular fibrillation is not dangerous in itself in the presence of adequate myocardial oxygenation.

Physiologic Basis for Surgical and Other Procedures. After coronary artery occlusion, the ventricles are likely to go quickly into irreversible ventricular fibrillation or the hearts that survive this critical period may remain hypodynamic, with resulting limited work tolerance and large residual cardiac pain. It is presumed that the hearts of such individuals have too much infarcted tissue and too little collateral development. A most important problem is the evaluation of the effectiveness of surgical (and physiologic) procedures designed to stimulate collateral anastomoses in this situation.

Before assessing the physiologic implications of such surgical therapy for coronary occlusion, one must take cognizance of the natural large compensatory mechanisms that protect the heart before and after coronary artery occlusion. Apparently, the heart adopts the prophylactic measure of setting up or enlarging anastomoses between its own coronary arteries without the stimulus of coronary occlusion or insufficiency. In this connection, fundamental observations show that in the presence of anemia, cor pulmonale, cardiac hypertrophy, or valvular disease the incidence of intercoronary collateral anastomoses in injected human hearts is increased greatly over that in the normal human heart and, actually, in some instances, their frequency of appearance may approximate that with coronary artery occlusion or narrowing.[12] A similar augmentation of the collateral bed of the coronary artery in pigs and dogs with induced anemia has been observed by injection and physiologic studies.

Our knowledge of compensatory changes in the coronary system following coronary occlusion is derived largely from the dog and pig.[4, 13] If blood is allowed to flow from a major branch (descendens or circumflex) of the left coronary artery distal to the point of its occlusion, this retrograde flow approximates within the first few minutes only 2 or 3 ml./min. of fully oxygenated blood that arises in

the other coronary artery. If the heart survives, the retrograde flow of oxygenated blood increases quite slowly to double within 48 hours and, within four weeks, to approximate the normal inflow into that coronary artery before its occlusion. In this situation, injection studies show that the intercoronary arterial collateral vessels increase greatly in size, number, and length, and most collateral flow comes from the right coronary artery or from the other major branch of the left coronary artery. Whether the increase in collateral flow is through pre-existing, nonfunctioning collateral vessels or through newly formed channels, or whether the latter ever develop, has never been determined.

This slow development of collateral circulation for as long as a month after occlusion may mean that a relatively small amount of collateral flow will maintain a viable myocardium, for many of these hearts survive with minimum infarction. This contrasts with the situation in the femoral and carotid arteries, in which collateral functioning reaches large values within one to two days after artery ligation.

Table 1 illustrates some of the attempts made to enhance the collateral circulation in the presence of coronary insufficiency.[14] In this regard we are greatly indebted to Dr. Beck and associates for making available to us much unpublished data. Some of these procedures have been applied to selected patients after coronary occlusion and who have had persistent angina pectoris and gross work disability. Improvement is reported in many instances. The criterion of success for any of the maneuvers should be a considerable reduction in the number and size of infarcts. These parameters are difficult to evaluate in human beings. In the dog, however, information on these points has accumulated from a number of laboratories including our own, and some of the trends are set forth in table 1. Ligation of a major ramus (circumflex or descendens) of the left coronary artery alone causes a 70 per cent mortality within the first hour, and chronically there is considerable infarction. If partial or complete occlusion of the coronary sinus or its arterialization immediately precedes acute ligation of the coronary artery, the immediate mortality is reduced considerably. Chronic ligation of the coronary sinus, arterialization of the coronary sinus, or myocardial implantation of an internal mammary artery followed by coronary artery ligation also leads to a significant reduction in mortality and in the number and size of

TABLE 1.—*Surgical and Physiologic Maneuvers in the Normal Heart and in the Heart Following Coronary Artery Ligation*

Experiment	Surgical situation	Ligated coronary artery ramus		No previous coronary artery ligation	
		Mortality	Infarction	Anatomic collateral vessels	Retrograde flow
Acute	Coronary sinus open	70%	—	—	3 ml./min.
	Coronary sinus pressure increased	↘	—		
	Coronary sinus ligated				
	Aorta-sinus shunt				
Chronic	Coronary sinus open	70%	Gross	—	—
	Coronary sinus ligated	↘	↘	↗	↗
	Aorta-sinus shunt				
Chronic	Internal mammary artery imbedded in myocardium	↘	↘	↗	—
Chronic	Application of extracardiac tissue to myocardium—muscle, lung, intestine, pedicle skin flap	↘	—	↗	—
Chronic	Application of mechanical and chemical irritants to myocardium—abrasions, gauze, mica, phenol, talc, silver nitrate, asbestos	↘	↘	↗	↗
Chronic	Anemia	—	—	↗	↗
Chronic	Sham operation	—	—	↗	↗

in arcts. Application to the epicardium of various types of extracardiac tissue and of mechanical and chemical irritants in a chronic preparation also reduces mortality and infarction in the presence of subsequently induced occlusion of the coronary artery. Accordingly, it is deduced that these prior surgical maneuvers give sustained (and in the case of coronary venous maneuvers, immediate) protection against ligation of a major branch of the coronary artery.

If a heart can be benefited by such surgical procedures, then it should be helpful to have in mind the possible ways in which they could protect the heart. This consideration should be aided by reference to figure 1 in which are shown schematically the anatomic details of the coronary circulation. In the case of the coronary venous maneuvers, the protection could arise immediately from the creation of pressure relationships that promote passage of blood from the superficial coronary veins in retrograde fashion through the capillary bed and into the deep drainage system. Possibly, with these and other procedures, the benefit could arise from a small increase in blood flow through intercoronary and extracardiac collateral circulation established by the surgical procedures. Finally, the cardiac improvement could arise from the early protection that the procedures might give against ventricular fibrillation in the presence of coronary occlusion, and without change in collateral blood flow, thus allowing time for additional collateral circulation to develop and sustain the heart.

Let us now consider the available experimental data that may help to indicate which of these three physiologic possibilities is used to protect the heart against coronary occlusion in the presence of surgical maneuvers. There are no critical experiments to indicate that with the acute coronary venous maneuvers protection against fibrillation is supplied by blood flowing in a retrograde direction from coronary vein to coronary capillary to ventricular cavity. Acute perfusion of the coronary sinus with arterial blood at or near mean aortic pressure, or acute ligation of the coronary sinus, in each case being followed by acute ligation of the left coronary ramus, is characterized by venous congestion of the left heart with an increased coronary venous pressure equal or equivalent to the aortic pressure, a diffuse myocardial hemorrhage (with the exception of the septum which remains pink in color), and a sizable reduction in left coronary inflow.[4] When the peripheral portion of the occluded coronary artery is permitted to bleed externally, the volume of back flow (15 to 26 ml./min.) of highly reduced blood is increased greatly over that following acute ligation of the coronary artery alone; this blood can be shown to have traversed the capillary bed of the occluded coronary artery in a reverse direction. There is no proof, however, that when the ligated coronary artery is not permitted to bleed externally, flow from the superficial coronary veins will be diverted through the capillary bed of the left myocardium. Actually, the development of extreme myocardial embarrassment, together with the fact that most of left coronary artery inflow and the blood entering the coronary sinus from the shunt can now be recovered in the anterior cardiac veins of the right ventricle, strongly suggests, but does not prove, that the deep ventricular drainage channels are not used.

Hearts in which either chronic ligation or arterialization of the coronary sinus has been combined with chronic ligation of the coronary artery have given no further evidence on the possibility of utilizing deep drainage channels of the heart or developing superficial collateral circulation. The coronary hemodynamic status is very similar to that following chronic ligation of the coronary artery alone; that is, the retrograde flow into the occluded coronary artery, which was initially highly venous, is now large in volume, arterial in type, and arises in the other coronary arteries.[4]

Studies[15] on dogs prepared by the Beck technic with a long-term aorta-coronary sinus shunt have given some positive evidence on the mode of protection against subsequent acute ligation of the coronary artery. If, up to five weeks after the second stage of the operation, a major coronary branch is occluded acutely and then its peripheral end is permitted to bleed, flow from the graft through

the collateral bed is considerable and the blood is highly unsaturated. This collateral flow with the graft open is greater than with it clamped, thus indicating that the graft continues to function. However, when the fistula is clamped acutely, collateral blood flow from the acutely closed coronary artery is now arterial in type and exceeds in volume the 2 to 3 ml. draining from an acute ligation of the coronary artery alone. Dogs studied in this way after more than five weeks and up to 1 year after coronary sinus arterialization show still further increase in collateral flow; the blood is now arterial and clamping of the graft does not affect retrograde flow, indicating that the graft has lost functional contact with the coronary bed. Most of the blood can be shown to come from the other coronary arteries, and its volume is far in excess of that which obtains in the normal dog in which a coronary ramus has been acutely ligated. In addition, injection studies in such hearts show an increase in the anatomic vascular bed. These observations, recently confirmed, suggest that arterialization of the coronary sinus has stimulated intercoronary artery collateral development which functions for some time in the presence of nonligated coronary arteries. As indicated in table 1, there is also considerable evidence to suggest that a similar augmentation of anatomic and functional collateral vessels follows the chronic induction of the various maneuvers indicated, including chronic anemia and sham operations. However, one must emphasize that with none of these procedures is the injected anatomic collateral bed or the retrograde flow of the order of magnitude observed with chronic ligation of the coronary artery alone. With chronic ligation of the coronary artery, this back flow approximates 60 to 80 ml./min.; with the coronary venous maneuvers, 12 ml./min.; with the other procedures, 8 to 9 ml./min.; with acute ligation of the coronary artery alone, 3 ml./min.

From the preceding discussion, it would appear that a number of surgical procedures give a certain degree of immediate and sustained protection against subsequent ligation of a major coronary ramus. Chronic coronary venous maneuvers, local application of myocardial irritants and of extracardiac tissue, and induction of anemia cause considerable development of anatomic collateral vessels and, apparently, also of functionally significant coronary artery anastomoses, as shown by the considerable increase in retrograde flow when a coronary artery branch is now acutely ligated and permitted to bleed. However, one must emphasize with equal vigor the uncertain aspects of these experiments. Our analysis demonstrates only that collateral development occurs on the arterial side of the coronary circuit and presumably at the arteriolar level, but it does not necessarily show that the blood collected from retrograde bleeding of the centrally occluded coronary artery has traversed the capillary bed of that artery when the artery is not permitted to bleed. If it did traverse the capillary bed, it could at most supply about 7 per cent of the oxygen normally available to that region. If it is this volume of oxygen that gives protection against fibrillation and death, then the factor of safety supplied by the maneuvers is small, for in a heart with an acutely ligated coronary artery alone the estimated oxygen supply to the potentially infarcted zone is 3 per cent of normal, and most of these hearts die. The measurement of change in capillary blood flow following these maneuvers that might yield conclusive proof of the functioning of the collateral bed, to our knowledge, has never been made. In the case of such procedures as coronary sinus ligation and arterialization or application of epicardial irritants, it does not seem to be possible to do this experimentally. However, the effectiveness of a skin pedicle flap, an artery implant, or an intestinal loop in promoting capillary flow through the potentially infarcted myocardium might be tested in the chronic situation by observing the change in coronary sinus flow before and after clamping of the extracardiac potential source of blood. Actually, in our laboratory in 2 dogs with chronic skin pedicle flaps applied to the left ventricle, subsequent clamping of the pedicles did not change the coronary sinus flow. This might seem to be a critical experiment, since there is no question about the establishment of vascular continuity between extracardiac tissue and the myo-

cardium; nevertheless, the beneficial effect of the graft may still be attributable to its acting as a bridge between the branches of one coronary artery and those of another, so that clamping of the extracardiac tissue would not alter flow of the coronary sinus. The fact that an equivalent intracardiac collateral development appears to follow a sham operation, also raises the question of the specificity of any of these maneuvers. Since in most instances death follows coronary artery ligation within 24 hours, we must still entertain seriously the third physiologic possibility mentioned earlier: that the benefits of reduced mortality and infarction arise in part from the protection that the procedures themselves might give against ventricular fibrillation in the presence of coronary occlusion (that is, without an immediate increase in retrograde flow), thus giving additional time for collateral circulation to develop and sustain the heart.

Since these surgical procedures afford protection to the dog heart against subsequent coronary artery ligation, it is possible that they might protect the human heart if used prophylactically. However, it does not necessarily follow that they will be of positive benefit to human beings with occlusive coronary artery disease. This view arises from a number of considerations, chief of which is that in these experimental studies coronary artery ligation was always preceded by the surgical maneuver, whereas in the human being, there is time after acute coronary artery occlusion for natural maximal collateral development before the surgeon attempts to arterialize the coronary sinus.

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ABSTRACTS

CONGENITAL ANOMALIES

Schoenmacker, J., and Stratman, E.: The Coronary Vessels and the Myocardium in Congenital Cardiovascular Lesions. Arch. f. Kreislaufforsch. **22:** 153 (May), 1955.

Histologic and angiographic postmortem studies are reported in 60 cases with various types of congenital heart disease (47 cyanotic) and in 37 controls. In general, the shape and size of a congenitally malformed heart are determined by the location and severity of the lesion and the extent of associated intracardiac and extracardiac shunts. The coronary vessels usually do not differ in their over-all distribution from normal, but they are wider (including the capillaries) and reveal many intracardiac and extracardiac anastomoses. Histologically, the arterial wall shows abnormalities consisting in doubling of the muscular layer and fissures apparently secondary to contraction of the muscular arteries during death. Cardiac veins are hypertrophic in all cases with pressure elevation in the right heart, as similarly found in mitral stenosis. This may be a factor responsible for the rare occurrence of myocardial fibrosis in congenital heart disease. In 53 instances, numerous nervous elements were found in the myocardium, usually in aggregates, in contrast to their rarity in the control cases.

The authors conclude that dilated and hypertrophic coronary arteries and veins, wide capillaries, well-developed anastomoses and a marked tendency to hypertrophy of the right ventricle are the morphologic factors which, in young individuals with congenital heart disease, prevent development of chronic congestive heart failure.

PICK

Gubbay, E. R.: Isolated Congenital Dextrocardia. Am. Heart J. **50:** 356 (Sept.), 1955.

The author presents a case of isolated dextrocardia with a functionally normal heart. In isolated dextrocardia, if the arch of the aorta is left-sided and P_1 is erect, then the chambers of the heart are not inverted. The spatial relations of the spatial QRS and T vectors on the frontal plane are also discussed in this condition. A second case, apparently of isolated dextrocardia, is described and is contrasted with the general pattern obtained.

RINZLER

Kohout, F. W., Silber, E. N., Schlichter, J. G., and Katz, L. N.: The Dynamics of the Eisenmenger Complex. II. Am. Heart J. **50:** 337 (Sept.), 1955.

A study was made of 20 cases of the Eisenmenger syndrome, subjected to catheterization. The physiology of the Eisenmenger syndrome may be summarized briefly as consisting essentially of interventricular septal defect wherein the muscular contraction is the major dynamic factor, with a large number of as yet undefined factors in addition. An explanation of the pathophysiology of the Eisenmenger syndrome is untenable merely on a simple hydraulic principle of two circuits of unequal resistance. The increased pulmonary resistance present in this anomaly is of purely fortuitous occurrence. It is most probable that inflammatory changes or a co-existent, congenital anomaly is responsible for the derangement of the pulmonary circuit. The rapidity and degree of these changes determine whether any given case presents a partial or complete picture of the Eisenmenger syndrome or remains an uncomplicated interventricular septal defect.

RINZLER

Pinto, I. J.: The Clinical Syndromes in Paten Ductus Arteriosus. Am. Heart J. **50:** 1 (July) 1955.

Cases of patent ductus arteriosus were classifie according to auscultatory findings. The size of th ductus was evaluated according to the acousti findings and the urgency for surgery indicated. I

cases belonging to group A, type 1, there is a continuous murmur at the pulmonary area, indicating a shunt across the ductus both in systole and diastole. The volume of flow across the shunt is not sufficient to cause an apical diastolic murmur. Operation in these cases is indicated because of the danger of subacute bacterial endocarditis.

Cases in group B, type 1a, have an atypical murmur at the pulmonary area. This alteration of the continuous murmur is the result of an elevated pulmonary arterial pressure. These cases should be operated on as early as possible, since pulmonary hypertension is progressive and terminates in right heart failure. Surgical correction has, in some cases, led to a return of the pulmonary arterial pressures to normal.

Cases in group A, type 2, and group B, type 2, have in common an apical diastolic murmur. This indicates a large volume of shunt across the ductus. In group A, type 2, the aortic-pulmonary pressure gradient exists both in systole and diastole, while in group B, type 2, the aortic-pulmonary pressure gradient permits a flow only in systole. Thus, a large shunt occurs in systole only. This could only result from the presence of a ductus of a large diameter. A diastolic murmur at the apex denotes a large left-to-right shunt through a large ductus. In infants belonging to this group, surgical correction is a lifesaving procedure. In all cases of patent ductus arteriosus with an apical diastolic murmur, surgical correction is an urgent procedure.

RINZLER

Van Lingen, B., and Bauersfeld, S. R.: The Electrocardiogram in Ebstein's Anomaly of the Tricuspid Valve. Am. Heart J. **50:** 13 (July), 1955.

The electrocardiograms of 8 cases of Ebstein's anomaly of the tricuspid valve have been studied. These were characterized by complete right bundle branch block in all cases, and by small deflections (R, R′, and R + S) in leads V_1 and commonly in leads V_2, V_3, V_4. Tall and prolonged P waves occurred commonly, and were considered to be evidence of right atrial hypertrophy and dilatation. Prolongation of the P-R interval and supraventricular tachycardia were also observed. It was considered that the small deflections of the QRS complex in the right chest leads were due to the thinness of the proximal chamber of the right ventricle, which is a characteristic and constant feature of Ebstein's disease. This feature of the electrocardiogram in Ebstein's anomaly is only rarely found in complete or incomplete right bundle branch block from other causes, and is believed to be of value in the diagnosis of this condition. The association of electrocardiographic evidence of right atrial hypertrophy in the absence of evidence of right ventricular hypertrophy (small R or R′ waves in the right chest leads) is uncommon in other types of congenital heart disease and is a characteristic feature of Ebstein's anomaly.

RINZLER

Ober, W. B., and Moore, T. E., Jr.: Congenital Cardiac Malformations in the Neonatal Period. An Autopsy Study. New England J. Med. **253:** 271 (Aug. 19), 1955.

The report is concerned with a review of 100 autopsies drawn from 1,665 examinations at the Boston Lying-in Hospital over a 23 year period during which 100,000 babies were born, and autopsies were performed on 60 per cent of those who died during the first month. The anomalies encountered most frequently were transposition of the great vessels, interventricular septal defect, cor triloculare and biloculare, coarctation of the aorta, endocardial sclerosis, interatrial septal defect, persistent truncus arteriosus and tetralogy of Fallot. Few lesions involved the pulmonic or aortic valves. Of the 100 cases studied, 64 were male and 36 were female. All 13 cases of complete transposition of the great vessels were males, as were 6 of 7 cases of endocardial sclerosis. Increased survival during the first month of life did not appear to be associated with any particular type of malformation. Of 9 stillborn infants, the primary lesion in 5 cases was a large interventricular septal defect. Seven infants, including 4 stillborn children, had severe anomalies of other systems in addition to the cardiovascular malformations. There were 11 cases of coarctation of the aorta, 6 of the infantile type, 3 of the adult type, and 2 with coarctation of the ascending aorta and arch; the ductus arteriosus was patent in all of them, and almost all of these infants died in congestive failure. In all 5 cases of fibroelastosis, one or more of the 4 valves were involved. Interventricular septal defect occurred as the only lesion in 6 cases and in association with other cardiac anomalies in 9 instances. There were 6 infants with interatrial septal defects, 4 of which were unassociated with any other cardiac anomalies. On the basis of clinical features it appeared difficult to predict the type of congenital cardiac anomaly to be found at autopsy in these infants dying in the neonatal period. Cyanosis seemed most intense in those infants with complete transposition of the great vessels without intracardiac shunts. Cyanosis was less constant in infants with tetralogy of Fallot or defect of the interatrial septum. The heart weight was nearly always increased in relation to body weight.

ROSENBAUM

Robicsek, F.: Post-Stenotic Dilatation of the Great Vessels. Acta med. scandinav. **151:** 481 (June 18), 1955.

Various studies were performed to determine the mechanism whereby poststenotic dilatation of vessels occurs, particularly as it is seen clinically in pulmonic stenosis and coarctation of the aorta.

Studies on models made of glass and of rubber showed no evidence of local rise in pressure in the area distal to the constriction. Catheterization studies in pulmonic stenosis and coarctation of the aorta have shown low pressures in the areas of poststenotic dilatation and in the adjoining undilated sections of the vessel involved. The characteristics of flow of fluid in a model of glass simulating aortic coarctation were studied, with a dye injected into the system at intervals.

It was found that (1) the fluid passes through the constricted and immediately subjacent parts of the system in the form of a homogeneous column (mechanical constriction is followed by a so-called dynamical constriction), (2) active turbulence can be seen in the poststenotic region and (3) the particles of fluid remain in the poststenotic region for prolonged periods of time and are in turbulent motion.

Histologic study of the vascular wall, from the zone of poststenotic dilatation, has disclosed that the elastic elements of the media are defective in parts, and there are extensive areas of increased fragility.

It has been observed that poststenotic dilatation is more apt to occur where the stenosis involves only a short section of the vessel and there is a sudden increase in the vascular lumen, whereas it is uncommon where the stenosis is of the infundibular type and there is a gradual increase in the vascular lumen.

It is concluded that in cases of localized stenosis of the great vessels, there is a considerable turbulence that leads to a loss of energy and causes extensive damage to the vascular wall. As a result of this turbulent flow, the elastic elements in the vascular wall distal to the stenosis are damaged, and the blood pressure in this area brings about dilatation at the site of reduced resistance.

ROSENBAUM

Steinberg, I., and Geller, W.: Aneurysmal Dilatation of Aortic Sinuses in Arachnodactyly: Diagnosis During Life in Three Cases. Ann. Int. Med. **43:** 120 (July), 1955.

Arachnodactyly (Marfan's syndrome) is a rare hereditary disease of unknown etiology. It is characterized by widespread malformations of the skeletal, cardiovascular, and ophthalmic systems. Medial degeneration of the aorta and, rarely, of the pulmonary artery is a constant finding. Aneurysmal dilatation of the ascending aorta, with dissection and rupture and aortic regurgitation and heart failure, is a frequent cause of death. Fibromyxomatous endocardial lesions are also common and may produce murmurs of valvular stenosis or regurgitation. The demonstration during life of an aneurysm in the sinus of Valsalva in a patient with arachnodactyly has hitherto not been reported. Angiocardiographic study of 3 consecutive patients with arachnodactyly disclosed aneurysmal dilatation of the aortic sinuses in each instance. The first patient, a man of 40 years, was asymptomatic in spite of cardiac enlargement of 6 years' duration. The second patient, a 47 year old woman, had sudden onset of chest pain followed by dyspnea and weakness; on examination, aortic regurgitation, mild congestive failure and enlargement of the heart were found. The third patient was also asymptomatic; a systolic apical cardiac murmur increased in intensity over a 6 year period; no enlargement of the heart was present, however.

WENDKOS

CORONARY ARTERY DISEASE

McQuay, N. W., Edwards, J. E., and Burchell, H. B.: Types of Death in Acute Myocardial Infarction. Arch Int. Med. **96:** 1 (July), 1955.

An analysis was made of 133 cases, in which the patients died of acute myocardial infarction in the hospital. Necropsy was performed in each case. The three major causes of death were myocardial failure, which occurred in 43 per cent, coronary failure, which occurred in 23 per cent and rupture of the heart, which occurred in 15 per cent. A factor influencing the occurrence of myocardial failure was previous myocardial infarction. Coronary failure, a term used to designate a syndrome of recurrent pain after acute infarction, but without recurrent infarction, occurred in 23 per cent of the patients. In this group, the acute infarct was subendocardial in a greater number of cases than in the entire series. Rupture of the heart was observed only in patients having transmural infarction. Women were predominant among those with rupture of the heart. This complication did not differ significantly in incidence between patients receiving anticoagulant therapy and those who did not. Major emboli occurred in 6 per cent of the patients. One half of these emboli were pulmonary and one half were systemic.

BERNSTEIN

Russek, H. I., Urbach, K. F., and Zohman, B. L.: Paradoxical Action of Glyceryl Trinitrate (Nitroglycerin) in Coronary Patients. J. A. M. A. **158:** 1017 (July 23), 1955.

For more than 75 years, no drug has proved superior to nitroglycerin in treatment of angina pectoris. On the other hand, clinical experience has proved that nitrites are not always followed by clinical improvement and may even cause untoward effects. The study of the effect of varying doses of glyceryl trinitrate (0.2 to 1.2 mg.), 1/300 to 1/50 gr. on electrocardiographic response to standard exercise was undertaken in 158 patients with coronary disease who showed consistently positive changes in control studies. With the dose of 0.4 mg. (1/150 gr.) given sublingually 5 minutes before exercise, 131 patients (83 per cent) responded favorably. Eleven patients, or 7 per cent, showed no

ignificant effect from the drug. Sixteen patients (10 er cent) demonstrated even greater abnormalities han were apparent in the electrocardiographic ecords of control tests. The study appears to indiate that individualization of dosage is important. n the 16 patients who responded paradoxically to he drug when given exercise tests, the following obervations were made: 1. Such electrocardiographic hanges induced by glyceryl trinitrate were similar o those that were recorded in the performance of he Master two-step test. 2. Paradoxic response to lyceryl trinitrate is caused by venous pooling in the ower extremities, diminished venous return to the eart, and reduced coronary blood flow in spite of oncomitant coronary vasodilatation. In some cases, hange from the recumbent to the erect posture produced electrocardiographic alterations similar to hose evoked by the drug. Elastic bandages on the ower extremities prevented the changes occurring n standing. 3. The action of glyceryl trinitrate on he venous system may have therapeutic application in the prophylaxis and treatment of acute congestive heart failure where decrease in venous return and diminution in heart size are important therapeutic objectives. 4. It should be appreciated that the drug may have adverse effects in angina pectoris. The optimum dosage for most patients is 0.2 to 0.3 mg., or 1/300 to 1/200 gr., sublingually. Acute myocardial infarction is more than a theoretic danger from overdosage during treatment of the anginal attack.

KITCHELL

Rinzler, S. H., Travell, J., and Karp, D.: Detection of Coronary Atherosclerosis in the Living Animal by the Ergonovine Stress Test. Science **121:** 900 (June 24), 1955.

The ergonovine stress test has been said to produce electrocardiographic changes indicative of coronary artery disease in patients with angina. In this study, rabbits were fed a high-cholesterol diet and were subjected to the ergonovine stress test at periodic intervals.

Extensive occlusive coronary atherosclerosis, with myocardial damage, was present in the cholesterol-fed rabbits as compared to the control animals. There was a strong correlation between electrocardiographic changes after ergonovine and the presence of coronary atherosclerosis. The authors suggest that the ergonovine test may be a new experimental procedure for the study of coronary artery disease in the living animal.

WAIFE

CONGESTIVE HEART FAILURE

Wohl, M. G., Shuman, C. R., and Alper, C.: Nutritional and Metabolic Aspects of Congestive Heart Failure. Arch. Int. Med. **96:** 11 (July), 1955.

The ability of the heart to fulfill its function in maintaining circulation can be materially influenced by diet. By appropriate dietary regulation, using subcaloric feedings in acute failure, the work of the heart is reduced, thereby increasing blood flow, lowering the blood pressure, slowing the heart rate, increasing vital capacity, and inducing diuresis. The restriction of dietary sodium is a basic step in avoiding fluid retention due to impairment of renal sodium excretion. Effort should be made to assure adequate potassium tissue stores by the periodic administration of potassium salts to cases of chronic heart failure. Supplemental vitamin therapy is required, as shown by the presence of low tissue vitamin stores in heart failure, and the high rates of vitamin excretion during diuresis. The assurance of an adequate protein intake is urgently needed in the hope of avoiding the evidences of protein malnutrition that eventually appear in so many of these patients.

BERNSTEIN

Bernath, J., Guillemot, R., Samuel, P., and Heim De Balsac, R.: Vena Cava Inferior Ligation in Congestive Heart Failure. Am. Heart J. **50:** 112 (July), 1955.

One hundred patients with cardiac decompensation were treated by ligation of the inferior vena cava. Dyspnea was improved immediately after operation. Hepatomegaly and peripheral edema then disappeared. The major indications for the procedure were mitral disease and combined mitral and aortic disease. Absolute contraindications were considered to be cardiac disorders with high output (chronic cor pulmonale, thyrotoxicosis) as well as certain valvular lesions with marked restriction of the circulation (as in advanced aortic stenosis). The mortality during the first postoperative year was 23 per cent. The survival rate, after the first year was 60 per cent; after the second, 49 per cent; after the third, 40 per cent; and after the fourth and fifth, 33 per cent.

RINZLER

Olmstead, E., Cassidy, J. E., and Murphy, F. D.: The Use of Beer in the Low-Salt Diet with Special Reference to Renal Disease. Am. J. M. Sc. **230:** 49 (July), 1955.

Beer with a high-caloric and low-sodium content was used in the low-salt diet of patients with renal disease. The patients under observation on calculated diets, with and without beer, included those with chronic glomerulonephritis, Kimmelstiel-Wilson's disease, and malignant hypertension. The fluid intake was restricted to 2000 ml. daily. The nutritional content of beer (1150 ml.) is given as calories (480), protein (3.20 Gm.), carbohydrate (50 Gm.), alcohol (40 Gm.), sodium negative. The beer-added diet was well tolerated and was regarded as more palatable than the regular hospital low-sodium diet. There was no clinical or laboratory evidence of increased deterioration in the renal process.

The added beer did not provide clinical improvement. One patient receiving the beer-added diet for one year showed no untoward effect from this regimen.

SHUMAN

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, AND BALLISTOCARDIOGRAPHY

Carlsten, A., Clemedson, C. J., and Hultman, H. I. S.: The Electrocardiogram of Rabbits in Blast Injury. Acta physiol. scandinav. **33:** 243 (June), 1955.

The electrocardiographic changes in blast injury of rabbits are variable. An instantaneous, transient, and often pronounced, sinus bradycardia and a lowering of the voltage are found in almost every case. They are due to reflexes from the damaged lungs and partly from the carotid sinus. Intracardiac damage may be responsible for the low voltage, also the premature beats, depression of S-T segment, and atrial fibrillation. Some of the changes are not manifested until several minutes to some days after the detonation.

AVIADO

Bruce, R.: Ventricular Tachycardia following Exercise in a Case of Angina Pectoris. Brit. M. J. **1:** 892 (April 9), 1955.

A 46 year old man, with angina pectoris and a normal electrocardiogram before and after exercise test, developed what was almost certainly ventricular fibrillation (flutter, if you will), with an average cardiac rate of 330 per minute. This reverted promptly without specific measures.

MCKUSICK

Huppert, V. F., and Berliner, K.: The Intraventricular Conduction Time (QRS Duration) of Ventricular Premature Systoles. Cardiologia **27:** 87 (Fasc. 2), 1955.

In 148 cases, in all age groups, the contour and QRS duration of premature systoles of ventricular origin were analyzed. Neither widening nor bizarreness of QRS is essential to diagnose ventricular premature systoles. The QRS duration is sometimes difficult to determine because of superposition of the sinus P wave on the initial or terminal portion of the ectopic beat. The patient's age has an influence on the QRS duration of the premature beats. In no case under 21 years, was QRS more than 0.15 sec., and in none over 66 years was it shorter than 0.10 sec. No relationship could be established between QRS duration of ventricular premature systoles on the one hand and their degree of prematurity or the duration of QRS in the normal beats, on the other hand.

PICK

Mumenthaler, M.: Electrokymography and Its Application in the Study of Gallop Rhythm. Cardiologia **26:** 321 (Fasc. 6), 1955.

Methods of investigation are reviewed concerning the mechanical aspects of the heart action, with special reference to electrokymography. In 10 of 20 personally observed cases with gallop rhythm, electrokymograms showed certain distortions that coincided with the pathologic third heart sound. The hypothesis is advanced that during certain phases of the cycle, the heart muscle is physiologically predisposed to abrupt changes in tone. In the failing heart, hemodynamic or muscular (metabolic) factors aggravate or facilitate the occurrence of this tonus alteration in the same portion of the cycle. The additional sound in gallop rhythm is thought to represent the acoustic manifestation of such abrupt changes in tone.

PICK

Schott, A.: Disorders of Auricular Rhythm Associated with Bundle Branch Block Simulating Ectopic Ventricular Tachycardia. With Observations on Intermittent Bundle Branch Block. Cardiologia **26:** 353 (Fasc. 6), 1955.

Three cases of supraventricular (atrial) tachycardia, with impairment of intraventricular conduction, which might have been interpreted erroneously as paroxysmal ventricular tachycardia, are presented. In the first case atrial flutter with ventricular response varying between 2:1 and 3:1 was associated with an intermittent type of intraventricular block. In the other two cases, comparison with previous or subsequent records established the diagnosis of intermittent intraventricular block in the presence of atrial fibrillation.

The three criteria considered characteristic of a ventricular origin of a paroxysmal tachycardia, namely, irregularity of the ventricular rhythm, widened QRS complexes, and a slower independent atrial rhythm, can no longer be considered conclusive. The cases presented are examples invalidating the first two criteria, whereas the third is contradicted by numerous instances of proved supraventricular tachycardia reported previously in the literature.

PICK

Zanchi, M., and Lenègre, J.: Histologic Lesions of the Tawara-His System and Its Branches. Cardiologia **27:** 1 (Fasc. 1), 1955.

Histologic lesions of the conduction system in 29 cases with disturbances of A-V and intraventricular conduction were studied with a dissection technic described previously. In the A-V node and common bundle, both vascular and inflammatory lesions have the morphologic characteristics encountered in other parts of the myocardium. Rheumatic lesions of the left bundle branch are circumscribed, and

ɔcated at or near the bifurcation, whereas vascular schemic or fibrotic) lesions tend to affect the periphral part of the bundle, and often lead to its compression, sometimes by development of calcifications. The right bundle branch may be affected in s entire course by either inflammatory or vascular sions. The latter represent extensions of confluent ɔptal infarctions, or may be part of a diffuse sclerois of subendocardial or deeper myocardial layers.

A comparative study of electrocardiographic alerations and histologic changes in the conduction ystem shows a good correlation as to the time of volution and the morphologic type of the lesion.

PICK

Gross, D.: The Auricular T wave and Its Correlation to the Cardiac Rate and to the P Wave. Am. Heart J. **50:** 24 (July), 1955.

Displacement of the P-R interval, the only visible section of the atrial T wave in the normal electrocardiogram, has been studied with special reference to the cardiac rate. Displacement of the P-T_a segment is determined by the cardiac rate and the area of the P wave. The P-T_a segment is practically invisible at cardiac rates below 70 beats per minute; it becomes increasingly visible from 71 to 90, and at rates over 90, it is constantly present. The average displacement of the P-T_a segment increases with increasing cardiac rates. The height and the area of the P wave present a direct correlation both with the incidence and the degree of displacement of the P-T_a segment, independently of the cardiac rate. With P waves less than 400 microvolt seconds, the P-T_a segment is visible only occasionally; above the level of 800 microvolt seconds, a P-T_a segment is constantly visible. In the middle zone, from 400 to 800 microvolt seconds, the P-T_a segment becomes increasingly visible. Displacement of the P-T_a segment is a physiologic phenomenon and is found constantly in the normal electrocardiogram under established conditions, and is therefore devoid of clinical and pathologic significance.

RINZLER

Rosenbaum, M. B., and Lepeschkin, E.: Bilateral Bundle Branch Block. Am. Heart J. **50:** 38 (July), 1955.

An electrocardiographic diagnosis of bilateral bundle branch block can be made in rare instances in which conduction in the branches is not completely interrupted and the degree of block in one of the branches is less than in the other on some occasions and greater on others. This allows the patterns of right and left bundle branch block to appear alternately or intermittently in the same patient. Two new cases of this type are reported and seven similar ones in the literature are discussed. While the incidence of definitely proved bilateral bundle branch block is very small, the great incidence of unilateral bundle branch block suggests that many cases of complete A-V block, attributed to a conduction disturbance in the A-V node or the common stem of the bundle are, in reality, caused by bilateral bundle branch block. In seven of the nine cases of definite bilateral bundle branch block, alternation of the right and left bundle branch block patterns was present at some time. The most probable explanation was considered to be 2:1 block in one of the branches and a constantly delayed conduction in the other branch. Conduction in the branches behaves in the same way as in the rest of the conduction system. True bilateral bundle branch block must necessarily prolong the A-V conduction time. The form of the ventricular complex is determined by the branch with the greater degree of block, while the conduction delay in the branch in which the block is less important determines the lengthening of the P-R interval. This must be so because the stimulus reaches the ventricles through the less affected branch. In true bilateral bundle branch block, the intrinsicoid deflection of the ventricular complex is delayed only on the side of the chest corresponding to the more affected branch, and is within normal limits on the opposite side. Cases in which the intrinsicoid deflection is delayed over both ventricles probably represent an association of true bundle branch block with an intraparietal-conduction disturbance of the contralateral ventricle.

RINZLER

Christensen, L. K., and Andersen, E. W.: Reciprocal Rhythm with Prolonged Ventricular Bigeminy. Acta medica scandinav. **151:**.465–472 (June 18), 1955.

An elderly man was observed over a period of seven years. On several occasions he had atrioventricular rhythm with reciprocal beating. On one occasion, during and after anesthesia for a urologic procedure, there was constant bigeminy and reciprocal rhythm for 12 hours. On one occasion intervening reciprocal beats produced a trigeminal rhythm. The bigeminal reciprocal rhythm is said to be the longest recorded period of such rhythm. It is said that the factors leading to atrioventricular rhythm also lead to reciprocal rhythm when they are acting more intensely. Increased vagal tone, which intensifies the retrograde block in the atrioventricular node to the point that the impulse returning to the ventricles is delayed until it finds the ventricle in a responsive state, is considered the most important factor producing this disorder. In the electrocardiograms recorded in this patient, the retrograde P waves were upright in leads II and III, instead of negative, as is usually the case in atrioventricular nodal rhythm, except as the anesthesia deepened. The authors express the opinion that the P waves in nodal rhythm need not be inverted in leads II and

III, but need only to be changed from the normal atrial complex.

ROSENBAUM

Chelton, L. G., and Burchell, H. B.: Unusual RT Segment Deviations in Electrocardiograms of Normal Patients. Am. J. M. Sc. **230:** 54 (July), 1955.

The clinical and electrocardiographic data were analyzed in 100 patients with tracings in which the RT segments showed an elevation of 1 mm. or more in standard or precordial leads. Such records may be interpreted as indicative of heart disease or pericarditis; however, adequate clinical correlation and subsequent tracings may establish the absence of abnormal changes. The elevation frequently presented is a U-shaped connection between the R and T waves, usually maximal in V_4 and V_5 positions, occasionally as high as 3 mm. or more. The QT index and other electrocardiographic periods were normal. The mean spatial vector of sustained systolic potential was directed inferiorly, anteriorly, and to the left in all cases.

No demonstrable heart disease was found in 82 per cent. The remaining 18 per cent had heart lesions that were not believed to be responsible for this type of tracing. There were 46 per cent of the group who presented functional symptoms. Anterior chest wall pain was noted in 32 patients. It is essential that this normal pattern be distinguished from that associated with pericardial or myocardial diseases. Exercise causes the elevated RT segment to return to the baseline. The elevation may be explained by early repolarization of the subepimyocardium before completion of ventricular depolarization.

SHUMAN

Schott, J., Jacobi, M., and Wald, M. A.: Electrocardiographic Patterns in the Differential Diagnosis of Progressive Muscular Dystrophy. Am. J. M. Sc. **229:** 517 (May), 1955.

Electrocardiographic findings in 9 cases of progressive muscular dystrophy are presented. Of these, 6 are of the pseudohypertrophic type. The significant electrocardiographic feature in this series was the occurrence of high voltage QRS complexes in one or more of the precordial leads. In 4 of the 6 cases of the pseudohypertrophic type, the voltages exceed normal limits; while in the other 2, the maximum normal values are approached. Cases published previously disclose similar high voltage complexes. In the facioscapulohumeral type of muscular dystrophy, the QRS complexes are of normal amplitude. Tall QRS complexes are regarded as an additional differential feature distinguishing between the two groups of dystrophic disease.

SHUMAN

HYPERTENSION

Grollman, A.: The Effect of Various Hypotensive Agents on the Arterial Blood Pressure of Hypertensive Dogs. J. Pharmacol. & Exper. Therap. **114:** 263 (July), 1955.

Hypotensive agents, which have been introduced during recent years for the treatment of hypertensive cardiovascular disease, have been administered to rats and dogs with experimentally induced renal hypertension. The dosages of adrenolytic and ganglion blocking agents, veratrum and rauwolfia alkaloids, necessary to lower blood pressure in such animals, are relatively much higher than that tolerated by humans. Hypertensive animals afford a supplementary method for screening potential hypotensive agents.

AVIADO

Lewitus, Z.: Transient Hypertension Associated with Acute Polyneuritis. Acta medica orientalia. **14:** 104 (April), 1955.

Thirty cases of polyneuritis, admitted to the Beilinson Hospital during the years 1940 to 1953 were surveyed. Among these, 12 were found to have had a transient hypertension during their illness (an incidence of 40 per cent). A control group of 26 cases of infectious mononucleosis, of a similar age distribution, showed only a 15 per cent incidence of hypertension. The possible connection between polyneuritis and the rise of blood pressure is discussed.

BERNSTEIN

Miller, S. I., Livesay, W. R., Snyder, H. B., and Moyer, J. H.: Treatment of Hypertension with Hexamethonium Alone and in Combination with Apresoline. Texas J. Med. **49:** 516 (July), 1953.

Sixty-three patients with severe essential hypertension were treated with hexamethonium administered orally. Forty-three responded with a 20 mm. fall in mean blood pressure. Thirty-two patients continued therapy for an average of 10 months. Apresoline, combined with hexamethonium, improved the blood pressure response of 10 patients, 6 of whom failed to respond to hexamethonium alone. Drug-fastness occurred only twice, and, in general, the dose of hexamethonium did not have to be significantly increased with continued therapy.

Side effects, chiefly due to parasympathetic blockade and excessive hypotensive response, were minimized by careful regulation of dosage. These effects decreased with prolonged therapy. Marked improvement in the cerebral and cardiac complications of hypertension occurred with prolonged therapy. No serious accidents have occurred. Oral hexamethonium, alone or in combination with Apresoline, is a practical and effective therapeutic

agent for the treatment of moderate or severe hypertensive cardiovascular disease.

BERNSTEIN

Huber, H. B.: Combined Chlorpromazine-Rauwolfia serpentina Therapy in Essential Hypertension. J. A. M. A. **158:** 730 (July 2), 1955.

Seventy-five patients with hypertension were given a capsule containing chlorpromazine (15 mg.) and *Rauwolfia serpentina* (whole root, 50 mg.) 3 times daily. No other medication was prescribed for the patients during the course of treatment, and the patients were observed by the same observer at weekly intervals. More than 85 per cent of the patients with mild hypertension showed demonstrable significant lowering of blood pressure. More than 70 per cent of the patients with moderate hypertension were benefited, and more than 60 per cent with severe hypertension were improved. Only 1 patient was unable to tolerate the preparation because of marked somnolence. Blood pressure readings of almost all the patients given placebos during the course of therapy increased to original levels after 10 to 14 days of placebo therapy. After reinstitution of combined chlorpromazine-rauwolfia therapy, improvement was again observed in about 2 weeks. In an addendum to the article, it was noted that a total of 350 patients with essential hypertension have been treated, and results were even more promising when the dosage schedule was 25 mg. of chlorpromazine combined with 50 mg. of rauwolfia 3 or 4 times daily. After 18 months of therapy, no jaundice or other side effects were observed in any of the 350 patients.

KITCHELL

Moulton, R., and Willoughby, D. A.: A Short Laboratory Screening Test for Phaeochromocytoma. Lancet **2:** 16, (July 2), 1955.

The effect of untreated human urine on the blood pressure of the cat was observed. After neutralization the urine was injected intravenously into cats anesthetized with Nembutal. Blood pressure was recorded by means of a recording mercury manometer. Comparisons with standard solutions of adrenalin and noradrenalin in normal urine were made.

Most samples of urine had little effect on blood pressure. If a response at least equal to that from 0.1 μg./ml. of adrenalin or noradrenalin was obtained, the following were tested: (a) Boiling the alkalinized urine, to which ferric chloride was added, should greatly diminish the pressure response; (b) Intramuscular ergotamine tartrate altered the shape of the pressure-response curve with an inconstant effect on the height of the curve; (c) Dibenzylene completely inhibited the pressor effect; (d) Intravenous mepyramine maleate potentiated the effect of adrenalin and noradrenalin, but completely antagonized any response to histamine, which was the "contaminant" causing the greatest difficulty.

Among 250 patients, 7 cases of pheochromocytoma were discovered or confirmed.

MCKUSICK

Friedman, S. M., Friedman, C. L., and Nakashima, M.: Effect of Pitressin in Experimental Renal Hypertension in the Rat. Am. J. Physiol. **180:** 469 (March), 1955.

Pitressin lowers blood pressure in rats made hypertensive by renal compression or partial nephrectomy. Daily injections produce a cumulative effect. There is also a delayed depressor response 7 to 9 hours after injection of 4 international units (IU) in rats hypertensive from desoxycorticosterone acetate (DCA). A series of 2 IU injections accomplishes like results. The delayed response is not observed in rats made hypertensive by renal compression. With the larger doses, the delayed response is seen in rats made hypertensive by subtotal nephrectomy. It is not detected when lower doses are used. Poor renal function in subtotally nephrectomized rats may explain the 2 latter observations.

OPPENHEIMER

Gaunt, R., Antonchak, N., Miller, G. J., and Renzi, A. A.: Effect of Reserpine (Serpasil) and Hydralazine (Apresoline) on Experimental Steroid Hypertension. Am. J. Physiol. **182:** 63 (July), 1955.

Rats were administered desoxycorticosterone acetate and salt in quantities that produced hypertension and death in all subjects in 71 days. There was some fall in blood pressure and prolongation in survival time when either hydralazine or reserpine was administered. The combination used for as long as six months was observed to reduce blood pressure while at the same time renal and vascular pathologic changes were delayed or prevented. These animals grew faster and survived for three times as long as untreated controls.

OPPENHEIMER

Kolff, W. J., and Page, L. H.: Influence of Protein Diets on Development of Renoprival Hypertension in Dogs. Am. J. Physiol. **181:** 580 (June), 1955.

Hypertension resulting from nephrectomy was accentuated by overhydration with an electrolyte solution resembling extracellular fluid. However, intermittent peritoneal lavage did not prevent the production of hypertension. High-protein diets containing 4 to 6 Gm./Kg. of casein per day were fed to dogs. The high-protein diets produced a minimal increase in renoprival hypertension. Medial arteriolar necroses and focal myocardial

necroses were more frequent and more severe in those fed high-protein diets.

OPPENHEIMER

Kolff, W. J., and Page, I. H.: Renoprival Hypertension and Antirenin. Am. J. Physiol. **181:** 575 (June), 1955.

Antirenin titers of dogs were actively and passively elevated. Subsequent bilateral nephrectomy and overhydration were still able to produce hypertension. Furthermore, the hypertension of normally hydrated renoprival dogs was not reduced by antirenin. Antirenin did not prevent arteriolonecrosis or multiple focal hemorrhagic necroses in the myocardium of renoprival hypertensive dogs. In all these previously mentioned cases, pressor responses of small and medium doses of renin were blocked. The responses to large doses of renin resembled those obtained with angiotonin. Also, elevation in blood pressure obtained from transplanted kidneys, which were made acutely ischemic, was greatly reduced. It is concluded that the hypertension of bilateral nephrectomy and the observed associated vascular changes cannot be assigned to residual or extrarenal renin.

OPPENHEIMER

Masson, G. M. C., Del Greco, F., Corcoran, A. C., and Page, I. H.: Pressor Effects of Subcutaneously Injected Renin in Rats. Am. J. Physiol. **180:** 337 (Feb.), 1955.

There is a slight rise in blood pressure subsequent to subcutaneously injected renin on conscious rats. These effects are not always present under amytal anesthesia. Bilateral nephrectomy potentiates renin effects in unanesthetized rats. This is also true if rats were pretreated with desoxycorticosterone acetate (DCA) and salt. Renin-induced pressor effects may play a role in the diuresis and proteinuria that follow injection of this substance into normal rats. These same pressor effects may be operative in the vascular lesions produced by renin after administration of DCA and salt.

OPPENHEIMER

Andreae, E., and Smith, F. E., Jr.: The Effect of Reserpine on Renal Plasma Flow in Hypertension. Am. J. M. Sc. **230:** 45 (July), 1955.

The effect of oral reserpine upon renal plasma flow in a group of 15 hypertensive patients was evaluated by means of para-aminohippuric acid clearance determinations before and after administration of the drug. There was less than 10 per cent change in 13 patients, which was within the limit of accuracy of the test. The blood pressure changes observed were minimal. In 2 patients, decreases of 18 per cent and 33 per cent, respectively, in renal plasma flow, were detected following treatment.

SHUMAN

Markowitz, M., Koik, J. V., Hick, F. K., and Grissom, R. L.: Hexamethonium, Hydralazine and Rauwolfia Serpentina Therapy in Hypertension. Am. J. M. Sc. **229:** 486 (May), 1955.

The effects of rauwolfia alone and in combination with hexamethonium and hydralazine were evaluated in 66 patients having various degrees of hypertensive disease. The results of therapy in 20 patients with mild hypertensive disease receiving rauwolfia alone for an average of 10.5 months, revealed a reduction of the diastolic pressure of at least 15 mm. Hg in 14 patients. Side effects included "stuffy" nose, sleepiness, increased appetite, and depression. Nineteen patients with severe hypertensive disease received a combination of the three drugs in appropriate dosage for an average of 14 months, and achieved an average reduction of blood pressure of 25 mm. Hg diastolic.

Side effects of hexamethonium included constipation, postural hypotension, dry mouth, and blurred vision. Thirteen patients with malignant hypertension were given the combined therapy. Of the 6 patients still living, 5 were white women whose nonprotein nitrogen was nearly normal initially. The 4 Negro men in this group died. Because of increased sensitivity to postural changes, leading to syncopal episodes, hexamethonium was found difficult to use in patients previously treated by sympathectomy. There were 10 deaths in the 66 hypertensives, of which 7 were Negro men. In certain patients, the reduction of blood pressure worsened the clinical status of the patients; however, in others, dramatic improvements, including the reversal of papilledema were obtained.

SHUMAN

Moyer, J. H., Hughes, W., Dennis, E., Beazley, H. L., and McConn, R.: Results with a Combination of Rauwolfia and Adrenergic Blockade in the Treatment of Hypertension. Am. J. M. Sc. **230:** 33 (July), 1955.

Treatment of 47 patients with varying degrees of hypertension with rauwolfia plus adrenergic blockade was reported. Rauwolfia plus phenoxybenzamine was compared with this combination plus protoveratrine. A significant hypotensive effect is considered as a mean blood pressure reduction of 20 mm. Hg, or more, which was achieved in 74 per cent of the first group (rauwolfia and phenoxybenzamine), and in 82 per cent of the second (above plus protoveratrine). However, the former group was considered to have a slightly more severe hypotensive process. The requirement for phenoxybenzamine was much less when given with rauwolfia than when given alone; also the orthostatic hypotensive effect was less with the combination. The principal side effects, seen in nearly all patients in this series, consisted of nasal congestion, sedation, fatigue, dizziness, bradycardia, increased appetite, and ortho-

s atic hypotension. The combination of rauwolfia and] henoxybenzamine, with or without protoveratrine, (an be effective in the treatment of patients with s vere grades of hypertensive disease. The former : gent blocks vasoconstrictor impulses centrally, ' hile the latter blocks peripherally, providing a] otent combination for reducing hypertensive blood] ressures.

SHUMAN

tuppy, L. J., and Tober, J. N.: Treatment of Hypertension with Reserpine (Serpasil) Alone and in Combination with Hydralazine (Apresoline). Angiology **6:** 253 (June), 1955.

Eighty-three hypertensive patients were treated ith reserpine for periods of 3 to 12 months. In 15 f these patients hydralazine was also administered. o controls were employed beyond pretreatment nowledge of the patient's symptomatology and lood pressure range. The authors conclude that eserpine is an excellent hypotensive drug, and that ide reactions are few in number and minor in nature.

WESSLER

PATHOLOGY

Elster, S. K., Tuchman, L. R. and Horn, H.: Cardiac Hypertrophy and Insufficiency of Unknown Etiology. Bull. New York Acad. Med. **31:** 475 (June), 1955.

A series of 10 cases is described in which there was cardiomegaly and intractable heart failure, which at necropsy could not be explained on the usual causes of cardiac enlargement such as coronary artery disease, rheumatism, congenital defects, pulmonary disease, collagen disease, etc. There were 7 males and 3 females, ranging in age from 24 to 53 years. Prominent in the clinical picture was the rapidity of the course, intractability to therapy, low systolic pressure, intermittent fever and cardiac arrythmias. Premortem studies were extensive and failed to provide any clues as to etiology. At necropsy, the hearts were enlarged and there was uniform hydrocardial hypertrophy and areas of necrosis and scarring with secondary areas of an inflammatory reaction. No etiologic clue was provided at necropsy. In the reported discussion of the paper, it was pointed out that the measurements made during cardiac catheterization of one individual with this syndrome during life that the characteristics physiologically did not suggest nutritional deficiency such as beriberi or anemia or hyperthyroidism. Furthermore, it was pointed out that this condition is seen in greater frequency in the Negro than in the white individual.

HARVEY

Cohen, G. U., Peery, T. M. and Evans, J. M.: Neoplastic Invasion of the Heart and Pericardium. Ann. Int. Med. **42:** 1238 (June), 1955.

In an analysis of 1,007 consecutive autopsies performed during a 57-month period at George Washington University Hospital, 65 tumors metastatic to the heart, pericardium or both, were found among 315 malignant tumors of all kinds, an incidence of 20.6 per cent. Diagnosis was made prior to death in three patients and suggested in two others. Tumors of the breast, bronchus, the lymphoma group and malignant melanoma accounted for about three fourths of the cases with cardiac metastasis, which is in agreement with the experience of others. The development of one or all of the triad of cardiac failure, cardiac arrhythmias or cardiac compression in patients known to have malignant disease should suggest the possibility of metastases to the heart or pericardium. It would appear from this and other recent studies in the literature that neoplastic invasion of the heart is more frequent than was formerly believed, and should be given consideration in the differential diagnosis of heart disease.

WENDKOS

Ferguson, D. J., Berkas, E. M., and Varco, R. L.: Process of Healing in Experimental Pulmonary Arteriosclerosis. Proc. Soc. Exper. Biol. & Med. **89:** 492 (July), 1955.

Pulmonary vascular lesions were induced in dogs by anastomosing a systemic artery to the pulmonary artery. Within two weeks, the arterioles showed hypertrophy of the media, followed by progressive obliteration of the lumen due to intimal proliferation, which resembled those seen with some types of pulmonary hypertension in humans. After removal of the shunt and re-anastomosis of the pulmonary artery to its proximal stump, there was little regeneration in 3 months, but after one to two years, there was slow re-establishment of patency, chiefly by recanalization. The mechanical factors (increased flow and pressure) play an important role in the etiology of pulmonary vascular lesions.

AVIADO

Calvert, R. J., Nardell, S. G., and Raeburn, C.: Angiopathies in Acrosclerosis. Angiology **6:** 129 (April), 1955.

A case of acrosclerosis with calcinosis (Thibierge-Weissenbach syndrome) is described, in which the major arteries to the extremity were found to be occluded. The sclerodermatous process had involved skin, vessels, and nerves, as well as all the collagenous tissue of the extremity.

WESSLER

PATHOLOGIC PHYSIOLOGY

Williams, M. H., Jr., and Towbin, E. J.: Magnitude and Time of Development of the Collateral Circulation to the Lung after Occlusion of the

Left Pulmonary Artery. Circulation Research **3:** 422 (July), 1955.

Direct measurements were made of the collateral (bronchopulmonary) flow to the left lower lobe of the lung after ligation of the lobar artery. The flow immediately after ligation ranged from 4.4 to 9 ml./min., but one year after such ligation, the flow increased, ranging from 68 to 376 ml./min. This increase in collateral flow confirms vessel injection studies, which have demonstrated that bronchopulmonary anastomoses are exaggerated after occlusion (by disease or experimentally induced) of the pulmonary artery.

AVIADO

Daley, R., McMillan, I. K. R., and Gorlin, R.: Mitral Incompetence in Experimental Auricular Fibrillation. Lancet **2:** 18, (July 2), 1955.

In dogs, the acute initiation of atrial fibrillation caused change in the shape of the systolic portion of the atrial pressure curve (obliteration of the mid-systolic dip), and evidence of A-V valvular incompetence in the form of regurgitation of Evans blue dye injected into the ventricle. These observations may explain the difficulties in interpreting the amount of regurgitation versus stenosis in the presence of atrial fibrillation, the reason being that there is indeed regurgitation with the arrhythmia. The studies corroborate the view that atrial systole is important in the closure of the A-V valves. When atrial systole is absent, at least slight regurgitation early in ventricular systole seems to occur.

McKUSICK

Frank, E. D., Kaufman, D., Korman H., Schweinburg, F., Frank, H. A., and Fine, J.: Effect of Antibiotics on Hemodynamics of Hypovolemic Septic Shock. Am. J. Physiol. **182:** 166 (July), 1955.

Intraperitoneal injections of fecal suspension result in septic shock that resembles hemorrhagic shock of long standing. Plasma in sufficient quantities to restore or prevent a deficiency in plasma volume does not prevent the deterioration and fatal outcome in septic shock. If antibiotics alone are administered before septic shock is produced, they do not prevent hypovolemia and hypotension, although death is prevented. The authors conclude that the hemodynamic hypovolemic disturbances in septic shock and in hemorrhagic shock are not necessarily fatal of themselves. Correction of bacterial action enables dogs to tolerate septic shock better.

OPPENHEIMER

Freis, E. D., Broida, H. P., Hufnagel, C. A., and Rose, J. C.: Effects of Varying the Output of a Mechanical Left Ventricle on the Circulation in the Dog. Am. J. Physiol. **182:** 191 (July), 1955.

In these experiments a mechanical diaphragm pump replaced the left ventricle. It was possible to vary rate and stroke volume independently. The mean arterial blood pressure was observed to vary as a function of minute volume rather than either stroke volume or rate. When minute volume remained constant but stroke volume was increased while the rate of pumping was reduced proportionately, there was no change in the mean pressure. Under these circumstances pulse pressure was increased. When the output of the mechanical left ventricle was increased there was a parallel increase in that of the intact right ventricle. This latter increase was brought about largely by an increase in stroke volume. Changes in pump output caused similar changes in pulmonary and systemic pressure-output curves. Blood storage without changes in venous pressure was observed with increased pump output. This excess of blood is apparently not stored in the lungs.

OPPENHEIMER

Lewis, L. A., Masson, G. M. C., Corcoran, A. C., and Page, I. H.: Effects of Renin on Serum and Urinary Proteins in Desoxycorticosterone or Cortisone-Treated Rats. Am. J. Physiol. **180:** 331 (Feb.), 1955.

In normal male rats, administration of renin increases proteinuria. The electrophoretic mobilities of these proteins are similar to those of normal serum. The action of desoxycorticosterone acetate (DCA) is similar to that of renin. On the other hand, cortisone causes a slight increase in urinary albumin. DCA depressed blood albumin levels, but cortisone lowered protein levels. Animals pretreated with cortisone or DCA were sensitized to renin-induced proteinuretic effects, and the appearance of a small peak, measured as albumin, corresponded with increases in serum polysaccharide concentration. Serum lipoprotein patterns were irregularly abnormal, and serum cholesterol was correspondingly altered in rats given DCA. Although the administration of cortisone and renin caused gross visceral hemorrhages and hypoproteinemia with fluid retention, there was no increase in blood cholesterol. It is the authors' opinion that renin increases capillary permeability generally, as is evidenced by the presence of proteinuria. Cortisone inhibits tubular athrocytosis of albumin. Steroids and renin increase blood cholesterol and lipoproteins by acute renal damage and consequent nephrogenic hyperlipemia.

OPPENHEIMER

Salpeter, M. M.: A Renal Vasotropic Factor Produced by Electroconvulsive Shock. Am. J. Physiol. **182:** 177 (July), 1955.

After electroconvulsive shock vasoexcitor material (VEM) appears in the general circulation of goats and rats. Significant amounts appear in 15 minutes in goats. The peak is reached in the first hour. Ligation of the renal pedicle in rats blocked

t ıe appearance of this sensitizing factor after elec-
t oconvulsive shock.

OPPENHEIMER

ashour, F., Winchell, P., and Reddington. J.: Myotonia Atrophica and Cyanosis. New England J. Med. **252:** 768 (May 5), 1955.

A man, aged 57 years, presenting the major clin-al features of diffuse muscular weakness, lenticular pacities, gonadal dysfunction manifest by hypo-netabolism and testicular atrophy is described. There was a family history of similar involvement n his father and two siblings. In addition to the sual features of myotonia atrophica, or Steinert's lisease, there was marked cyanosis. Cardiac cathe-erization and studies of the pulmonary function sug-ested that this cyanosis was related to weakness of he thoracic and diaphragmatic muscles, resulting in mpaired alveolar ventilation and incomplete oxygen saturation of the blood in the pulmonary capillary. The observations also suggested an additional fac-tor of direct shunting from pulmonary capillaries to pulmonary venules in atelectatic areas of the lungs. This opinion was evoked from evidence that the arterial oxygen saturation rose to only 86 per cent after breathing 100 per cent oxygen, and that x-ray studies of the thorax showed areas of linear atelec-tasis.

ROSENBAUM

Williams, M. H., and Toubin, E. J.: Magnitude and Time of Development of the Collateral Circulation to the Lung after Occlusion of the Left Pulmonary Artery. Circulation Research **3:** 422 (July), 1955.

The collateral blood flow to the left lower lobe of the lung was measured after occlusion of the left pulmonary artery in anesthetized open-chest dogs. Immediately after the ligation, the blood flow was found to range from 4.4 to 9 ml./min. The amount of flow varied with the height of the blood pressure, but with a given blood pressure, did not increase during the 2- to 4-hour period of observation. In dogs that had previously been prepared by ligation of the pulmonary artery, the collateral blood flow was found to be increased, ranging from 68 to 376 ml./min. at the end of approximately one year of chronic ligation of the artery.

SAGALL

Eisley, N. F., and Pritham, G. H.: Arterial Synthesis of Cholesterol in Vitro from Labeled Acetate. Science **122:** 121 (July 15), 1955.

Various concentrations of C^{14} (carboxyl) labeled sodium acetate were added to tissue minces of turkey aorta. After incubation, cholesterol was extracted. The data indicate that the aorta can convert ace-ate into cholesterol. Minced tissue (which con-ained intact cells) was more active in cholesterol ynthesis than whole tissue slices. Hog aorta was nore active than that of turkey. Although the con-version of C^{14} labeled acetate into cholesterol by aorta was quantitatively less than produced by liver homogenates from the same amount of ace-tate, aortic cholesterol synthesis may be an impor-tant factor in atherogenesis.

WAIFE

Hercus, V. M., McDowall, R. J. S., and Mendel, D.: Sodium Exchanges in Cardiac Muscle. J. Physiol. **129:** 177 (July), 1955.

Electrolyte changes in the environment have been shown to affect materially the activity of heart muscle. This study quantitated the sodium, potas-sium, and water exchanges in rat heart muscle under varying environmental conditions.

Rat ventricles were suspended in a bath. Various solutions were used in the bath and aeration was ef-fected with 5 per cent CO_2 and 95 per cent O_2 or with 5 per cent CO_2 and 95 per cent N_2. The tem-perature and pH were kept constant. The heart muscle was analyzed for Na^+ and K^+ by a flame photometer and extracellular water by the inulin-space method.

In normal Kreb's solution (143 mEq. Na^+/L. and 5.9 mEq. K^+/L., the cardiac muscle absorbed Na^+ and lost K^+. When the Na^+ in the bath was then lowered to 93 mEq./L., intracellular Na^+ fell. Na^+ extrusion was therefore postulated and thought to be a useful measure of pump activity.

With a low Na^+ concentration in the bath from the beginning, a smaller uptake of Na^+ occurred. It increased without any change in K^+ loss with increasing Na^+ concentration of the bath to 177 mEq./L. The inulin space was not affected by changes in the Na^+ content of the solution. The ad-dition of K^+ to the bath failed to produce any changes.

Stretching the muscle increased the inulin space and the extracellular water and decreased intra-cellular water. Intracellular K^+ levels increased while Na^+ levels remained constant, indicating ex-trusion of Na^+. Stimulation of the muscle lowered K^+ and failed to change Na^+. Anoxia increased Na^+ uptake and damaged the Na^+ extrusion mechanism. Stimulation of anoxic muscle increased Na^+ up-take because of this damage to the extrusion mech-anism.

Cardiac muscle in physiologic media took up Na^+ and lost K^+. Stretching the muscle caused Na^+ ex-trusion; this loss may contribute to the efficiency of stretched muscle. Anoxia damaged the Na^+ ex-trusion mechanism permanently.

WECHSLER

PHARMACOLOGY

Andrews, W. H. H., Hecker, R., Maegrath, B. G., and Ritchie, H. D.: The Action of Adrenaline, L-noradrenaline, Acetylcholine and Other Substances on the Blood Vessels of the Perfused Canine Liver. J. Physiol. **128:** 413 (June), 1955.

An improved technic was devised for perfusion of the canine liver, whereby the selective vascular action of physiologically active substances could be demonstrated. Adrenalin and noradrenalin consistently constricted the portal vein and hepatic artery, but the effect on the hepatic vein was variable. Acetylcholine regularly constricted the portal vein, especially when injected into the artery rather than into the venous system. Histamine dilated the artery, but produced intense constriction within the hepatic venous tree. This clarification of a previously confusing situation is an initial step in understanding the physiologic significance of hepatic vasomotor nerves.

AVIADO

Gruhzit, C. C., and Farah, A. E.: A Comparison of the Positive Inotropic Effects of Ouabain and Epinephrine in Heart Failure Induced in the Dog Heart-Lung Preparation by Sodium Pentobarbital, Dinitrophenol, Sodium Cyanide and Sodium Azide. J. Pharmacol. & Exper. Therap. **114:** 334 (July), 1955.

Although it is generally agreed that the primary effects of the digitalis glycosides are on the heart, little is known about the underlying biochemical processes. The magnitude of the positive inotropic action of ouabain in the dog heart-lung preparation was found to be inversely proportional to the severity of the failure induced by cyanide, azide, or dinitrophenol. Mild failure was readily reversed by ouabain, while severe failure did not respond to this cardiac glycoside. In a heart in severe failure, the positive inotropic action of epinephrine was not blocked. This suggests that different biochemical mechanisms are involved in the positive inotropic actions of the sympathomimetic amines and the cardia glycosides.

AVIADO

Haley, T. J., and Weinberg, S. J.: Comparison of Strophanthin-K and Tryptamine-Strophanthidin after Intraventricular Injection in Unanesthetized Dogs. Proc. Soc. Exper. Biol. & Med. **89:** 345 (July), 1955.

The intraventricular injection of these two glycosides was compared. Both compounds produce bradycardia and typical digitalis changes in the T wave of the electrocardiogram at low doses, and the usual manifestations of digitalis toxicity at higher doses. The rapidity of onset after such injection indicates that the effects had their origin in the central nervous system. Barbiturate anesthesia abolished these central actions.

AVIADO

Lanzoni, V., and Clark, B. B.: Antiarrhythmic Action of Ambonestyl. Circulation Research **3:** 335 (July), 1955.

Dogs with persistent ventricular tachycardia from a previous coronary ligation were given procaine amide and Ambonestyl (2-diethyl-aminoethylisonicolinamide). This new compound was as effective in suppressing the arrhythmia as procaine amide. Ambonestyl was pharmacologically more specific, since it produces less hypotension, a limiting factor in the intravenous use of procaine amide. Other differences of Ambonestyl from procaine amide are lack of depression in cardiac conduction, no elevation of diastolic electric threshold of the ventricle, and small increase in refractory period. The authors believe that the mode of action for this promising compound may be more closely related to factors controlling cellular transmembrane potentials, which do not manifest themselves in changes in threshold and conduction. Some alteration in cellular recovery processes may be implied from the increase in the refractory period.

AVIADO

Toh, C. C., Lee, T. S., and Kiang, A. K.: The Pharmacological Actions of Capsaicin and Analogues. Brit. J. Pharmacol. **10:** 175 (June), 1955.

This pungent principle from capsaicin has long been recognized as a powerful gastrointestinal stimulant and as a rubefacient. Intravenous injection of the compound causes powerful circulatory depression by stimulation of receptors in the heart and carotid bifurcation. It does not have a direct action on blood vessels. Like veratridine, capsaicin is a potent pharmacologic tool for studying the reflex circulatory activity of sensory nerve endings.

AVIADO

Walton, R. P., Richardson, J. A., and Brodie, O. J.: Cardiovascular Actions of Decaborane. J. Pharmacol. & Exper. Therap. **114:** 367 (July), 1955.

The industrial production of decaborane as a high energy fuel prompted its toxicologic study in dogs. In increasing doses (inhaled or injected). There was a progressive decrease in heart force, complicated by temporary hypertension, which was attributed to clumping of blood masses with obstruction of smaller vessels. The hypertension, in some instances, may have been due also to direct action on the adrenal glands. Progressive electrocardiographic changes included decrease in height of P waves, slow A-V nodal rhythms, occasional ectopic beats, and asystole.

AVIADO

Waud, R. A., Lansing, A. M., and Lewis, R. A.: The Effects of Veratrum, Dibenzyline and Hexamethonium on Blood Pressure as Studied with an Artificial Heart-lung. J. Pharmacol. & Exper. Therap. **114:** 271 (July), 1955.

These hypotensive agents were studied in the artificial heart-lung to segregate the factors involved in the fall in blood pressure. In a dog in which car-

liac output was maintained constant by substituting an artificial heart-lung, dibenzyline and hexamethonium produced a significant fall of arterial pressure, indicating that the peripheral resistance, rather than the heart, is the important factor. On the other hand, Veriloid did not lower the blood pressure when the cardiac output was similarly maintained constant. This fact was interpreted to mean that reflex cardiac depression is the major cause of the hypotension in control animals. The suggested, minor role of peripheral vasodilatation for veratrum alkaloids is contrary to reports of other investigators.

AVIADO

Drury, A., and Treadwell, C. R.: Effect of Epinephrine on Plasma Lipid Components and Interrelationships in Normal and Epileptic Humans. J. Clin. Endocrinol. **15:** 818 (July), 1955.

Normal adult and epileptic subjects showed the same concentrations of plasma lipid components in the postabsorptive state. However, the ratio of phospholipid to free cholesterol and the ratio of neutral fat to phospholipid were significantly lower in the epileptic group than in the normal group. One hour after the intramuscular injection of 0.4 mg. of epinephrine, the free, esterified, and total cholesterol concentrations in the epileptic group were significantly greater than the respective values in the normal subjects, and the neutral fat fraction in the normal group was significantly greater than in the epileptics. These changes resulted in significant alterations in the ratios. These different responses to epinephrine undoubtedly reflect differences in the metabolism of epileptic subjects.

CORTELL

Leusen, I., Demuster, G., and deWitte, J.: A Study of the Influence of Ro 2-3248 upon Cardiovascular Dynamics. Arch. internat. pharmacodyn. **52:** 147 (June), 1955.

The authors present studies on the effects upon cardiovascular dynamics in unanesthetized dogs, with and without section of the vagus nerves and carotid sinus, of Ro 2-3248 (Ilidar). This substance is the most potent of a group of antiadrenalin compounds, which are derivatives of Dibenamine. Cardiac rate, femoral arterial pressure, and electrocardiograms were measured. Cardiac output was measured and total peripheral resistance then calculated. Well controlled experiments were done. It was found that the substance, Ro 2-3248, in the anesthetized animal with carotid sinus sectioned, caused a reduction in arterial tension and thereby a fall in total peripheral resistance and a fall in cardiac output. Tachycardia established at the time of sectioning was not increased. In the intact animal there was only a slight fall in blood pressure and no appreciable change in cardiac output. However, tachycardia occurred.

HARVEY

Gorlin, R., and Robin, E. D.: Cardiac Glycosides in the Treatment of Cardiogenic Shock. Brit. M. J. **1:** 937 (April 16), 1955.

Three patients with the combination of pulmonary edema and shock on the basis of acute myocardial infarction and one with only shock were treated with cardiac glycosides in small doses intravenously. Dramatic clinical improvement followed. They recommend 25 to 50 per cent of the initial dose given to the average cardiac patient, because of apparently increased susceptibility to arrhythmias in the patient with myocardial infarction. They used ouabain in 3 patients, lanatoside C in the fourth. The absence of elevated systemic venous pressure should not be taken as an indication that myocardial failure will not benefit by digitalis.

MCKUSICK

Harris, A. S., and Bisteni, A.: Effects of Sympathetic Blockade Drugs on Ventricular Tachycardia Resulting from Myocardial Infarction. Am. J. Physiol. **181:** 559 (June), 1955.

Myocardial infarction was produced in dogs by two-stage ligation of the anterior descending artery at the level of the free edge of the left atrial appendage. The best results for reduction in the number of ectopic beats were obtained with Dibenzyline intravenously, Regitine when injected directly into coronary arteries, and Dibenamine intravenously. In the case of the last mentioned, large convulsant doses had to be used. Norepinephrine arrhythmias were demonstrated to resemble infarction arrhythmias more closely than those due to epinephrine.

OPPENHEIMER

Harvey, W. P., Berkman, F., and Leonard, J.: Caution Against the Use of Meperidine Hydrochloride (Isonipecaine, Demerol) in Patients with Heart Disease, Particularly Auricular Flutter. Am. Heart J. **49:** 758 (May), 1955.

The authors indicate that meperidine may exert an atropine-like action, and, when 100 to 150 mg. were given intravenously to 26 normal subjects, it caused an increase in the pulse rate by an average of 11 beats per minute, with 2 individuals having an increase over 30 beats per minute. Since atropine may quickly change the ventricular rate in atrial flutter from 85 to 170 beats per minute by going from a 4:1 to 2:1 response, the use of meperidine with its atropine-like action should be used with caution in atrial flutter. Such increases of ventricular rate in atrial flutter by meperidine are illustrated by case reports.

RINZLER

Tesoriere, H. S., and Lipson, H. I.: The Use of Procaine Amide (Pronestyl) to Accelerate Blood Transfusions in the Anesthetized Patient: Its Generalized Sympatholytic Effect without Hypotension. Am. Heart J. **49:** 770 (May), 1955.

Procaine amide, in doses of 0.5 to 1.0 Gm., was mixed with each 500 ml. of blood given as transfusions to anesthetized patients. The procaine amide accelerated the administration of the transfusion because local venospasm was prevented. Despite the spasmolytic effect the drug showed no hypotensive effect.

RINZLER

Loomis, T. A., and Krop, S.: Auricular Fibrillation Induced and Maintained in Animals by Acetylcholine or Vagal Stimulation. Circulation Research **3:** 390 (July), 1955.

By "sensitizing" animals with moderate doses of anticholinesterase drugs, the authors were able to induce atrial fibrillation of extended duration in the intact heart of unanesthetized normal dogs, goats, and monkeys after the intravenous administration of acetylcholine or other vagal stimulation. The rate of existing atrial fibrillation was found to increase with the injection of acetylcholine. Atrial fibrillation could be reinduced in the converted heart by additional injections of acetylcholine. Once the fibrillating state was induced, it could be maintained for long periods of time by proper continuous infusion or repeated injections of acetylcholine, or by electric stimulation of the distal end of the cut right vagus nerve. Induction of fibrillation was facilitated by depressing the normal sinoatrial nodal function by cold or crushing. Atropine was found to slow the rate of fibrillation, and small doses converted the rhythm to normal and prevented subsequent induction of fibrillation with acetylcholine.

SAGALL

Malinow, M. R., Battle, F. F., and Malamud, B.: The Pharmacology of Experimental Arrhythmias in the Rat. 2. Mechanism of Action of Nupercaine Hydrochloride. Arch. internat. pharmacodyn. **102:** 266 (July), 1955.

White albino rats were anesthetized with Nembutal, 6 mg./100 Gm., intraperitoneally, in 0.6 per cent solution. Ventricular flutter and fibrillation were induced by an intravenous injection of 0.2 ml./100 Gm. of a 10 per cent solution of calcium chloride. In another series of experiments the same arrhythmias were elicited by topical application of aconitine to the ventricles.

Injection of 0.5 mg./100 Gm. of nupercaine intravenously into rats before these arrhythmias were elicited did not prevent them. The arrhythmias induced by calcium chloride, as well as those caused by aconitine, appeared in 6 out of 10 experiments. Topically applied nupercaine, however, prevented the aconitine arrhythmias in 9 out of 10 animals if aconitine was applied on the same spot as the nupercaine. On the other hand, intrathecal injection of nupercaine prevented the appearance of the calcium arrhythmias in all 10 experiments.

These results support the previous conclusion made by the authors, that the calcium arrhythmias are neurogenic, while the aconitine arrhythmias are cardiogenic.

SCHERF

PHYSICAL SIGNS

Björk, V. O., Kjellberg, S. R., Malmstrom, G., Rudhe, U.: The Diagnosis of Mitral Insufficiency. Am. Heart J. **49:** 719 (May), 1955.

The authors present a technic for visualization of the mitral valves by angiocardiography, when the clinical findings and left heart catheterization suggest a dominating mitral insufficiency. This technic involves injection of the contrast medium through a needle of 1.0 mm. inner diameter, paravertebrally above the posterior end of the right ninth rib, and into the left atrium. It is possible to prove the diagnosis of a mitral insufficiency and avoid an exploratory cardiotomy by this method.

RINZLER

PHYSIOLOGY

Armin, J., and Grant, R. T.: Vasoconstrictor Activity in the Rabbit's Blood and Plasma. J. Physiol. **128:** 511 (June), 1955.

The vasoconstrictor properties, acquired by circulating blood as a result of hemorrhage, were investigated by transferring blood from any available vessel of a donor rabbit through a system of nonwettable tubes and taps to the central artery of the denervated ear of a recipient rabbit. The constrictor activity of plasma is usually slightly greater than that of blood owing to the release from platelets of a substance like 5-hydroxytryptamine (serotonin). Rapid bleeding of one third of blood volume of the donor rabbit increased the constrictor activity of its blood on the recipient's vessels. Adrenalectomy considerably reduced, but did not abolish, the constrictor activity of the blood. The source of extragrandular constrictors is undetermined but they may come from widespread sympathetic endings. The observations do not disclose the function of the constrictor substances in blood, but emphasize the importance of adrenalin and other constrictors in the circulatory compensation to blood loss.

AVIADO

Freedman, M. E., Snider, G. L., Brostaff, P., Kimelblot, S., and Katz, L. N.: Effects of Training on Response of Cardiac Output to Muscular Exercise in Athletes. J. Appl. Physiol. **8:** 37 (July), 1955.

In 3 long-distance runners, no alterations attributable to training were seen in the way the tissue de-

mands for an increased supply of oxygen were met during exercise. Increases in cardiac output, A-V oxygen difference, pulmonary arterial pressure, and ventilatory efficiency were for the most part similar to those reported by others. The only apparent effect of training was an increase in the maximum breathing capacity. The possibility has been suggested that chronic inflow-overload of the right ventricle might account in part at least, for the incomplete right bundle-branch-system block sometimes seen in electrocardiograms of athletes engaged in endurance sports.

AVIADO

Lindgren, P., and Uvnäs, B.: Vasoconstrictor Inhibition and Vasodilator Activation—Two Functionally Separate Vasodilator Mechanisms in the Skeletal Muscles. Acta physiol. scandinav. **33:** 108 (June), 1955.

The oblongata medulla is known to occupy a key position in the control of peripheral blood flow. Direct measurements of the venous outflow of the leg muscles of dogs and cats show that there are two vasodilator mechanisms. Vasoconstrictor nerves can be inhibited by depressor reflexes (electric stimulation of vagus or carotid sinus nerve) or by direct stimulation of the depressor area in the medulla. Vasodilator nerves can be stimulated directly at their origin from the motor cortex, or at their intramedullary outflow, which runs in close proximity to the bulbar motor pathways. The authors were unable to induce vasodilatation by both mechanisms simultaneously, a fact suggesting that they form two independent mechanisms. The sympathetic vasodilator outflow appears entirely unassociated with blood pressure-regulating mechanisms. It has been suggested that this vasodilator system takes part in the regulation of the muscle blood flow during exercise.

AVIADO

Ludemann, H. H., Filbert, M. D., and Cornblath, M.: Application of a Fluorometric Method for Adrenaline-like Substances in Peripheral Plasma. J. Appl. Physiol. **8:** 59 (July), 1955.

Fluorometric analysis of adrenalin in plasma from normal human subjects ranged from 0.0 to 0.4 μg./100 ml. Dogs poisoned with Parathion (cholinesterase inhibitor) to the extent of asphyxia, showed increased adrenalin content in blood only when anoxia was severe and when circulation had failed. Elevation was not seen during moderate depression of arterial oxygen saturation, but appeared abruptly in the terminal phase. This does not necessarily indicate that pressor substances were not being liberated throughout the course of asphyxia. It is probably due to the imbalance between rate of production and inactivation of adrenalin during severe asphyxia.

AVIADO

Roddie, R. A.: Effect of Arm Position on Circulation through the Fingers. J. Appl. Physiol. **8:** 67 (July), 1955.

The fingertips of seated subjects were supported at various levels above or below the sternal notch. The rate of heat elimination from the fingertips (to water measured calorimetrically) at all levels below the notch was slightly but significantly greater than that at the reference level. The increased rate of heat elimination from the dependent fingers is regarded as indicative of an unaltered or slightly increased rate of flow. In no experiment was there any evidence for a reduction of rate of blood flow, which has been interpreted by others from venous occlusion plethysmography.

AVIADO

Shadle, O. W., Moore, J. C., and Billig, D. M.: Effect of l-Arterenol Infusion on "Central Blood Volume" in the Dog. Circulation Research **3:** 385 (July), 1955.

Intravenous infusion of Arternol into anesthetized dogs caused an increase in the volume of blood in the heart and lungs, measured by dye or tracer dilution technic. Pressure in the pulmonary artery and left ventricle and rotameter flow in the vena cava were also increased.

The authors believe that these changes are due to shifting of blood from the constricted peripheral veins to the pulmonary vessels. The results do not exclude other possible explanations, such as Arterenol acting directly on pulmonary vessels, or the drug stimulating the heart directly and therefore increasing the pulmonary blood flow and blood volume.

AVIADO

Miller, H. C., and Smull, N. W.: Further Studies on the Effects of Hypoxia on the Respiration of Newborn Infants. Pediatrics **16:** 93 (July), 1955.

A well-planned and technically satisfactory experiment is presented, in which the effect of hypoxia was studied on newborn, premature, and full term infants. Newborn infants, both full term and premature, failed to respond by hyperventilation, either in rate or depth, during hypoxia induced by breathing 12 per cent oxygen. Premature infants several weeks old responded as the adult to hypoxia, with increase in respiratory rate and tidal volume. These studies further substantiate the author's previous hypothesis, that the chemoreceptors in the aortic arch and carotid body in the newborn are not as fully developed, or are not as sensitive as in older infants, or later on in life.

HARVEY

Brown, F. K., and Remington, J. W.: Arteriolar Responsiveness in Adrenal Crisis in the Dog. Am. J. Physiol. **182:** 279 (Aug.), 1955.

The arterioles of the vascular bed of the femoral artery were observed to function normally during

adrenal crises. They were compared to normal dogs, bled so as to have a comparable blood pressure. Pressor stimuli were more effective in normal dogs than in adrenalectomized subjects.

OPPENHEIMER

Cattell, M., and Gold, H.: Relation of Rhythm to Force of Contraction of Mammalian Cardiac Muscle. Am. J. Physiol. **182:** 307 (Aug.), 1955.

Test objects were isolated papillary muscles of the cat heart. Force and frequency of contraction were directly related. If rate changes were made abruptly, the force of contraction only gradually assumed that characteristic of the new frequency and the first few contractions were subnormal. Conversely, the first few contractions were augmented when the rate was decreased. The "staircase" phenomenon of Bowditch is similar; here the rate is changed from zero to a finite quantity. When single extra stimuli were placed close to a member of a regular series the next member was more forcible. The closer the interval, the greater the response; and the effect of a single extra stimulus lasted for several minutes. Rhythm or spacing of stimuli seemed more important than increased activity itself.

OPPENHEIMER

Dury, A., and Di Luzio, N. R.: Effects of Cortisone and Epinephrine Exhibition on Lipid Components and Phospholipid Turnover in Plasma, Liver and Aorta of Rabbits. Am. J. Physiol. **182:** 45 (July), 1955.

Rats were given single injections of epinephrine daily for 14 days. Another series received cortisone and a third a combination of cortisone and epinephrine. A control series was also provided. Plasma and liver lipids were increased by the exhibition of cortisone, with or without epinephrine. These same combinations increased plasma and liver phospholipid synthesis. Aortic lipid concentrations and aortic phospholipid turnover were unchanged by use of cortisone. Changes in plasma lipid after epinephrine were only moderate. Increased incorporation of isotopic phosphorus in the aorta was observed after epinephrine.

OPPENHEIMER

Frank, H. A., Frank, E. D., Korman, H., Macchi, I. A., and Hechter, O.: Corticosteroid Output and Adrenal Blood Flow during Hemorrhagic Shock in the Dog. Am. J. Physiol. **182:** 24 (July), 1955.

During the period of hemorrhagic shock adrenal blood flow was reduced to 15 per cent of control values. If the rate of adrenal blood flow was above 17 per cent of preshock flow, then rates of corticosteroid secretion were 60 to 100 per cent of controls. When the rate of adrenal blood flow fell below 17 per cent, the rate of corticosteroid secretion was 40 per cent or below. The output of corticosteroids in the control period or during shock was not correlated with the ability to tolerate shock.

OPPENHEIMER

Fregly, M. J.: Hypertension, NaCl Aversion and Polydipsia in Rats. Time, Course, and Relation to Age. Am. J. Physiol. **182:** 139 (July), 1955.

Renal hypertension was produced in rats by encapsulating both kidneys of rats with latex. In four weeks blood pressure was elevated and water intake increased. Younger rats were observed to have an aversion to NaCl eight weeks after operation, when blood pressure was maximum. Older rats developed the highest pressures, and salt aversion was inconsistent. Only in younger hypertensive rats were life spans shortened.

OPPENHEIMER

Katz, L. N., Katz, A. M., and Williams, F. L.: Metabolic Adjustments to Alterations of Cardiac Work in Hypoxemia. Am. J. Physiol. **181:** 539 (June), 1955.

In these experiments, cardiac oxygen consumption was well correlated with cardiac work, output of the left heart, and mean systemic blood pressure. Oxygen use of heart muscle for any increment of output was observed to be greater when these changes took place at elevated levels of blood pressure. The increase of oxygen consumption for a given rise in blood pressure was also greater at higher levels of cardiac output. The efficiency of the heart was a direct function of work, output of the left heart, and mean arterial blood pressure. There was no correlation with oxygen consumption. A low oxygen content was associated with increased cardiac efficiency. Use of oxygen was less when arterial oxygen content was low.

The level of cardiac work plays a role in the determination of cardiac oxygen consumption. This is true whether work is used to overcome increased pressure or to eject more blood. In some cases, the work of the heart increased as oxygen use grew less. At this time, pressure in the left atrium was better correlated with output of the left heart than either systemic arterial pressure or total cardiac work. However, changes in pressure in the left atrium did not correlate with heart oxygen use. On several occasions when there were unexplained changes in coronary flow, an increase in cardiac efficiency was observed. Useful work was thus increased from a fixed amount of oxygen.

Apparently the heart can alter the mechanism by which it obtains energy from oxygen. It appears that oxygen use depends on the level at which oxygen is supplied. The authors also present data that suggest a possible extracardiac mechanism (nonanoxic) that may control cardiac oxygen use in times of stress. It should be emphasized that in the *intact* animal, other factors than end-diastolic volume

control cardiac work and the manner in which energy is provided for such work.

OPPENHEIMER

Price, K. C., Hata, D., and Smith, J. R.: Pulmonary Vasomotion Resulting From Miliary Embolism of the Lungs. Am. J. Physiol. **182:** 183 (July), 1955.

Heart-lung-head preparations were used that could be quickly converted to heart-lung preparations. Barium sulfate was utilized to embolize the lungs. Pulmonary blood pressure and resistance increased abruptly, cardiac inflow decreased, and the right heart dilated. Death resulted in a few minutes. If the circulation to the head was eliminated at the height of the response, the pulmonary arterial pressure gradually subsided and the animals survived. Removal of the stellate ganglia and sympathetic chain down to the fifth thoracic level prevented the response to barium sulfate in the heart-lung-head preparation. Hexamethonium also eliminated the responses to the emboli. The presence or absence of the vagi was immaterial. Disseminated particulate emboli of the lungs produce marked pulmonary vasoconstriction mediated by pulmonary sympathetic fibers.

OPPENHEIMER

Ruhe, C. H. W., and Horn, R. H.: Circulatory and Respiratory Effects of Hypothermia Induced by Blood Refrigeration. Am. J. Physiol. **182:** 325 (Aug.), 1955.

Rabbits were cooled by blood refrigeration. If cold blood was returned to the head first, these animals died with higher heart and rectal temperatures than those in which the blood was first returned to the heart. Deaths were probably respiratory in both groups. At this time the brain temperature was 16 C. Rectal temperatures were unreliable measures of hypothermia, since they varied widely from heart and brain temperatures. The differences were more marked at the lower temperature levels. Electrocardiographic changes were observed to be a function of heart temperatures.

OPPENHEIMER

Stearner, S. P., Brues, A. M., Sanderson, M., and Christian, E. J.: Role of Hypotension in the Initial Response of x-Irradiated Chicks. Am. J. Physiol. **182:** 407 (Aug.), 1955.

Young chicks were exposed to 1000 r x-ray at 43 r/min. In the period immediately following, severe hypotension was observed. Birds that died in the first 24 hours had their major fall in pressure during the latter half of this period. The moderate earlier hypotension was not associated with any renal disturbances. There was complete anuria associated with the later severe hypotension. Although the kidney could be protected by shielding, anuria was not prevented during severe bouts of low blood pressure. Conversely, local irradiation of the kidney often produced enough kidney damage to cause fatal uricemia. Blood pressure was not changed by local irradiation. Sustained hemorrhagic hypotension failed to support normal renal function.

OPPENHEIMER

St. George, S., Freed, S. C., Rosenman, R. H., and Winderman, S.: Influence of Potassium Deprivation and Adrenalectomy on Potassium Concentration of the Myocardium. Am. J. Physiol. **181:** 550 (June), 1955.

Five week old male rats were fed a synthetic diet containing 0.006 per cent potassium and 0.6 per cent sodium. The latter is a normal amount. On this regimen potassium depletion was well advanced in five weeks. Rats were maintained on this diet for seven weeks, but one half of them had a bilateral adrenalectomy at the end of five weeks. All animals were sacrificed at the end of seven weeks. After adrenalectomy, both controls and those on the potassium-deficient diet were observed to have an elevated plasma potassium. Potassium of skeletal muscle was increased in adrenalectomized rats on potassium-deficient diets but not in controls. Neither experimental nor control adrenalectomized animals were demonstrated to have had any change in myocardial potassium. Myocardium may have more "bound" potassium than skeletal muscle does, and hence may be nonexchangeable.

OPPENHEIMER

Motley, H. L., and Smart, R. H.: Pulmonary Emphysema: Physiologic Factors in Diagnosis and Advances in Therapy. J. Am. Geriatrics Soc. **5:** 316 (May), 1955.

Pulmonary function measurements on 100 patients (aged 15 to 70 years), with pulmonary emphysema, show that: (1) the main difficulty is the increased resistance to moving air in and out of the lungs, and (2) the most characteristic abnormality in blood-gas exchange, is unequal alveolar aeration and perfusion.

Intermittent positive-pressure breathing of compressed air, together with suitable bronchodilators, is a valuable therapeutic procedure in the treatment of pulmonary emphysema. Following such treatment, an increase of activity is observed. Other routine measures may be used in conjunction with intermittent positive-pressure breathing of compressed air.

RINZLER

Philips, F. A., Brind, S. H., and Levy, M. N.: The Immediate Influence of Increased Venous Pressure upon Resistance to Flow in the Dog's Hing Leg. Circulation Research **3:** 357 (July), 1955.

The resistances to blood flow in the vascular bed of the denervated hind leg of the anesthetized dog

were determined over a wide range of intraluminal pressures, while maintaining a constant pressure difference bwteeen the arterial and venous ends of the circuit. When the arterial and venous pressures were increased in parallel fashion, higher absolute pressure values resulted in an increase of flow despite the constant arteriovenous pressure difference. The immediate influence, therefore, of elevated intraluminal pressure is a diminution of resistance to blood flow. This indicates that certain vessels, which offer significant resistance to blood flow, must be distensible and that passive dilatation of these vessels, due to the elevated internal pressure, is the initial and essential factor in reducing resistance.

SAGALL

Bergstrom, W. H.: The Participation of Bone in Total Body Sodium Metabolism in the Rat. J. Clin. Invest. **34:** 997 (July), 1955.

Sodium exists in the body in at least three phases: extracellular fluid, intracellular fluid, and in bone. This is a report of a study on rats, some of which were depleted of sodium by transperitoneal dialysis against ammonium chloride.

Extracellular sodium furnished 52 per cent of the sodium lost; intracellular sodium 20 per cent, and bone sodium 28 per cent. Acidosis produced a loss of sodium (carbonate) from bone whether or not there was a net loss of sodium from the body, and the presence of concomitant acidosis may be of crucial importance in the mobilization of bone sodium.

Little or no sodium retention observed (during oral or parenteral repair of acidosis and sodium depletion) could be assigned to the skeletal phase.

WAIFE

RHEUMATIC FEVER

Skillman, R. K., Spurrier, W., Friedman, I. A., and Schwartz, S. O.: Rheumatic Fever Activity Determination by Two Correlative Methods. Arch. Int. Med. **96:** 51 (July), 1955.

The principle of the antigen-antibody reaction has been the basis for numerous tests for the indentification of infectious diseases. Because rheumatic fever is associated with tissue reaction to group A beta-hemolytic streptococcus, identification of a specific bacterial antigen, or antibodies elicited by it, was studied as a means of ascertaining rheumatic fever activity.

Two methods of determination were employed: In one method, serum of patients with rheumatic fever was used as the antibody source and sheep red cells, coated with heat-killed group A beta-hemolytic streptococci which had been isolated from active rheumatic fever patients, were used as the source of antigen. Complement was added to produce hemolysis. The second method utilized Group A beta-hemolytic streptococcus antiserum obtained from rabbits as the antibody source. For the antigen source, erythrocytes of rheumatic fever patients exposed to the antigen for coating in vivo were used in an agglutination test.

Control studies of 77 varied patients, including those from whom alpha- and beta-hemolytic streptococci were isolated, showed no interference with either test method by other disease processes. Clinical data were correlated in 78 patients with rheumatic fever, most of whom were tested repeatedly. In most cases the titers in both test methods were elevated within the first few days of the active process. They then gradually subsided and disappeared as the process became inactive. The test results and the clinical status of the disease correlated well, although the height of the titer did not indicate the severity of the process.

These methods are of practical value in ascertaining activity or quiescence of a rheumatic fever process, as well as to distinguish rheumatic fever from other disease processes with similar clinical manifestations.

BERNSTEIN

Czoniczer, G., and Szabo, R.: Lanatoside Test as Proof of Rheumatic Carditis. Cardiologia **26:** 367 (Fasc. 6), 1955.

Among 36 patients with active rheumatic carditis, a significant transient prolongation of the P-R interval occurred in 11 patients, following intravenous injection of 0.08 mg of lanatoside C. This not the case in 70 controls, including patients with neurocirculatory asthenia, chronic valvular disease, and in patients in whom the active stage had subsided and the test had been previously positive. According to the authors, a positive lanatoside C test represents a certain way to establish the diagnosis of an active rheumatic carditis; a negative test, however, does not rule out activity.

PICK

Mandelbaum, H., and Mandelbaum, R. A.: Ballistocardiographic Studies in Patients with Probable Myocarditis. Am. Heart J. **49:** 661 (May), 1955.

Abnormal ballistocardiograms, as evidence of probable myocarditis, have been observed in rheumatic fever, disseminated lupus erythematosus, scleroderma, trichinosis, acute diffuse glomerulonephritis, in patients convalescing from infectious mononucleosis and pneumonia, and in instances of serum or drug sensitivity reactions. During the active stage of myocarditis, abnormal ballistocardiographic patterns were more frequent than electrocardiographic evidence of disease.

RINZLER

Stollerman, G. H., Rusoff, J. H., and Hirschfeld, I.: Prophylaxis against Group A Streptococci in Rheumatic Fever. New England J. Med. **252:** 787 (May 12), 1955.

Observations were made on 145 patients, studied for an average of 20 months per patient as outpatients, and 265 additional patients hospitalized at Irvington House, in the acute and convalescent stages of rheumatic fever, for an average follow-up period of 7.4 months. The patients were treated with monthly intramuscular injections of 1,200,000 units of benzathine penicillin G.

There were no recurrences of rheumatic fever in the 145 outpatients treated with intramuscular penicillin. This was in contrast to 2 recurrences in 111 patients in a control group treated with oral penicillin, and 5 recurrences in 73 patients in a control group given sulfadiazine. Of 2,716 throat cultures made in the group treated with intramuscular benzathine penicillin G, there were only 3 positive cultures for group A streptococci. This result contrasted with positive cultures in 19.3 per cent of untreated controls, 10.7 per cent in 75 patients receiving sulfadiazine, and 13.1 per cent in 99 patients receiving oral penicillin. The antistreptolysin 0 titer was determined every four weeks in the patients receiving intramuscular penicillin. A significant rise in titer occurred in only 3 patients. Of the total number of patients treated with monthly injections of benzathine penicillin, evidence of recurrence of infection with group A streptococci appeared in only 4 patients as either a positive culture, a rise in antistreptolysin 0 titer or both.

Of the patients studied, 71 had no clinical evidence of heart disease at the time of admission to the study and no subsequent signs of heart disease appeared in this group. Of 74 patients who were classed as having rheumatic heart disease at the beginning of the study, 8 were reclassified as having no heart disease at the end of the study, and in 3 patients there was some evidence of progression of the heart disease.

A total of 4871 injections were administered to the 410 patients. Deep muscular soreness and tenderness, lasting two or three days, was common. Transient low-grade fever, sometimes associated with local pain and tenderness, occurred in 10 per cent of the patients. Reactions, believed to be due to penicillin hypersensitivity, occurred in 5 patients. Three had mild, generalized urticaria, 1 had urticaria and angioneurotic edema, and 1 had a "serum-sickness" type of reaction. In the first 4 of these patients, injections of benzathine penicillin were resumed without further allergic manifestations. No attempt was made to resume penicillin prophylaxis in the last patient. Nonspecific, nonurticarial rashes appeared in 8 patients, but treatment was not interrupted. Two of the patients developed subacute bacterial endocarditis due to *Streptococcus viridans*. Both patients recovered following a six week course of crystalline penicillin G in large doses.

ROSENBAUM

ROENTGENOLOGY

Nesbit, T. E.: A Criticism of Renal Angiography. Am. J. Roentgenol. **73:** 574 (April), 1955.

The author suggests that the use of aortography be limited to those patients in whom information by other means is not available. This limitation is based on additional risk to the patient, added expense, and failure to provide significant information that might alter the course of treatment.

SCHWEDEL

Goetz, R. H., Nellen, M., Schrire, V., and Vogelpoel, L.: The Clinical Value of Angiocardiography. Angiology **6:** 63 (April), 1955.

The authors summarize their experiences in 387 angiocardiograms in 227 patients during a six-year period ending in 1953. The technics employed are described in detail. A simple inexpensive apparatus was used. Rarely was high speed angiocardiography necessary for diagnostic purposes. Hazards of the procedure are discussed. In the present series there was one fatal complication.

Angiocardiography has disproved certain erroneous assumptions concerning the composition of the normal cardiac contour that were based on the outline of the cardiac chambers found in the cadaver. The authors describe their findings in the normal heart and in hearts with a wide variety of congenital defects pictorially. They emphasize the efficacy of angiocardiography as an ancillary tool, facilitating more exact cardiac diagnosis. Its principal value lies in its aid to cardiac surgery.

WESSLER

SURGERY AND CARDIOVASCULAR DISEASE

Glover, R. P., McDowell, D. E., O'Neill, T. J. E., and Janton, O. H.: Mitral Commissurotomy in Relation to Pregnancy. J. A. M. A. **158:** 895 (July 16), 1955.

Rheumatic heart disease is responsible for 90 to 95 per cent of all organic cardiac lesions in pregnancy. Mitral stenosis, with or without other valvular lesions, is the common offender. Its most dangerous complication is pulmonary edema. The major effect of mitral commissurotomy is reduction of pulmonary vascular hypertension. In the first 500 consecutive commissurotomies performed by the authors, 5 were carried out during pregnancy. All 5 patients withstood the operation well and obtained marked functional improvement. Mitral commissurotomy may be carried out during pregnancy without harm to the mother or fetus. In these cases therapeutic abortion was avoided. The authors set up the following criteria to guide the selection of cases for mitral commissurotomy during pregnancy: 1. The operation is not advisable during pregnancy except in patients in stages 3 and 4 (New York Heart Association classification). 2. In patients in

stages 3 or 4, exploration of the valve and commissurotomy should be performed before therapeutic abortion and sterilization, since many patients may be so improved by surgery that such measures will not be indicated. 3. Commissurotomy is best done in the first trimester. As a rule, it is contraindicated after the thirty-second week and should be carefully weighed from the sixteenth to the thirty-second week. 4. The operation should be carried out during pregnancy in a patient of any functional grade if repeated emboli are endangering the life of the mother and fetus. 5. In patients over 35 years of age, or in those with atrial fibrillation, the condition of the valve found at surgery and the response following commissurotomy may be used to indicate whether the pregnancy represents too great a threat to the patient's life. Thus, the thoracic surgeon enters, with the obstetrician and the cardiologist, in the management of cases of mitral stenosis in pregnancy. The risk of commissurotomy and exploration of the valve to both mother and fetus in experienced hands is that of any abdominal or thoracic exploration during pregnancy.

KITCHELL

Likoff, W., and Bailey, C. P.: Ventriculoplasty: Excision of Myocardial Aneurysm. J. A. M. A. **158:** 915 (July 16), 1955.

In a 56 year old male patient with myocardial infarction, a large ventricular aneurysm, resulting from the infarction, was excised. Congestive heart failure was improved and the continuing pain of coronary artery insufficiency was relieved. Certain physical characteristics of ventricular aneurysm permit excision without undue blood loss or compromise of the size or continuity of the left ventricle. In view of the natural history of such lesions, it is suggested that excision be contemplated prior to the development of the serious consequences.

KITCHELL

Halmagyi, D., Robicsek, F., Felkai, B., Ivanyi, J., Zsoter, T., and Szucs, Z.: Hemodynamic, Renal and Metabolic Responses to Experimental Valvular Defects in Dogs. Acta cardiol. **10:** 93 (Fasc. 2), 1955.

Hemodynamic and pharmacodynamic aspects of 4 types of valvular lesions, produced experimentally in dogs, were investigated with the technic of cardiac catheterization. In mitral regurgitation, elevation of left atrial pressure was followed by a decline of pulmonary vascular resistance. Both pulmonary arterial and left atrial pressure decreased subsequent to the administration of sympatholytic agents. Pulmonary arterial pressure and resistance increased following production of tricuspid incompetence, or of pulmonary stenosis. In the former, it was in proportion to a concomitant elevation of right atrial pressure; in the latter, pulmonary hypertension proved proportional to the so-called stenosis index. In both groups, pulmonary arterial pressure and resistance fell following administration of sympatholytic drugs.

The results of these experiments suggest the presence of a neurogenic vasoconstrictive mechanism in the pulmonary circulation, mediated by receptor bodies in the right heart chambers.

PICK

Campbell, D. C., and Langston, H. T.: Intrathoracic Surgical Procedures in Patients Past the Age of Sixty. J. Am. Geriatrics Soc. **5:** 330 (May), 1955.

The authors report on major intrathoracic surgical procedures performed with gratifying success on 31 patients, 60 years of age or older. These operations were performed for known or suspected malignant conditions, and in 23 of the 31 patients, the presence of malignant disease was confirmed. Definitive surgical procedures were carried out in all but 8 instances and included all degrees of pulmonary resection. There were 2 deaths in the entire series, and 11 postoperative complications. Of 9 patients with known cardiac disease, only 4 suffered from heart failure after operation.

RINZLER

Vaughan, R. H., Deterling, R. H., Jr., and Smith, F. M.: Successful Excision of an Aortic Aneurysm Explored as a Paraspinal Tumor. New England J. Med. **253:** 15 (July 7), 1955.

In a man, aged 49 years, who had low back pain for one year, diagnostic studies disclosed a mass at the level of the twelfth dorsal vertebra, associated with destruction of the bodies of the eleventh and twelfth dorsal vertebrae. Preliminary diagnosis included tuberculosis, neoplasm, and Paget's disease. At the time of exploratory surgery, a biopsy was performed including a portion of necrotic bone, after repeated aspirations failed to produce pus or blood. The biopsy was followed by a gush of arterial blood, making it clear that the mass was an aneurysm. It was possible to isolate the mouth of the saccular aneurysm and to resect the aneurysm successfully. The celiac axis and superior mesenteric artery arose from the aorta anterior to the aneurysmal orifice. The patient made a good recovery and, after six months, returned to work as a chauffeur. He was free of pain, and working, two years following the operation. This case emphasizes the fact that an aneurysm may masquerade as an inflammatory mass or neoplasm, especially when located in the posterior mediastinum or in the paraspinal region. Both laminagraphy and needle biopsy failed to reveal the true diagnosis. Visualization technics might have been quite informative.

ROSENBAUM

Duff, R. S.: Effect of Adrenaline and Noradrenaline on Blood Vessels of the Hand before and after Sympathectomy. J. Physiol. **129:** 53 (July), 1955.

The present study attempts to assess the influence of sympathectomy on the reactivity of the blood vessels of the hand to noradrenalin and adrenalin. Vascular responses in the upper limbs of 10 patients, between the ages of 18 and 45 years, were studied before, and some days after, cervicothoracic sympathectomy. Blood flow in the hand was measured by venous occlusion plethysmography. Synthetic l-adrenalin tartrate or l-noradrenalin bitartrate in various concentrations was injected into the brachial artery.

Preoperatively, adrenalin caused vasoconstriction (mean of 16 per cent) if injected at a rate of ⅛ μg/min. Sympathectomy significantly increased the vasoconstriction at this rate to 44 per cent. It gave similar results at slower rates of infusion. This increased sensitivity occurred well before the first week.

Noradrenalin had a consistently greater constrictor effect than adrenalin at all dosage levels preoperatively. Sympathectomy significantly increased the vasoconstrictor effect of noradrenalin but this increased sensitivity (2 x) was not as great as with adrenalin (3 x).

Noradrenalin caused more vasoconstriction than adrenalin. Sympathectomy caused increased sensitivity to these drugs in some, but not all, individuals. This result conflicts with Cannon's theory that sympathectomy necessarily results in vascular supersensitivity. That preganglionic section causes greater sensitivity, was not confirmed; in this series ganglionectomy caused no more sensitivity than preganglionic section.

WECHSLER

Watts, D. T.: Epinephrine in the Circulatory Blood during Ether Anesthesia. J. Pharmacol. & Exper. Therap. **114:** 203 (June), 1955.

Plasma levels of epinephrine of rabbits under ether anesthesia, dogs under thiopental and ether anesthesia, and dogs under ether anesthesia alone, were determined by use of the bioassay method on rat uterus of Gaddum and Lambeck (1949).

The mean epinephrine content rose in plasma of rabbits under ether anesthesia and of dogs during ether overdosage, hypertensive episodes, respiratory depression, and cardiovascular failure with hypotension. In dogs during quiet ether anesthesia, there may be no detectable plasma epinephrine.

Ether anesthesia can increase plasma epinephrine levels in dogs and rabbits. Anoxia and hypotension are important and perhaps primary factors for initiating the release of this hormone. Epinephrine release is one of the defensive mechanisms against failing physiologic function during anesthesia. The increased epinephrine may account for the cardiac arrhythmia, hyperglycemia, and acidosis during ether anesthesia, and stresses the importance of maintaining adequate oxygenation and blood pressure.

WECHSLER

Collins, V. J., and Grantelli, A.: Controlled Hypothermia during Anesthesia in Human Adults. Use in Cardiovascular Surgery. Preliminary Observations. Angiology **6:** 118 (April), 1955.

Detailed protocols are presented of the physiologic alterations in 5 patients during controlled hypothermia for vascular surgery. The refrigerant was a solution of 30 per cent alcohol in tap water, pumped through pads encasing the patients. Best results were obtained by preceding the induction of hypothermia with general anesthesia. There were no significant anesthetic or operative complications. Because bleeding was minimal, the authors suggest that hypothermia deserves consideration in the management of patients under anticoagulant therapy who require surgery.

WESSLER

THROMBOEMBOLIC PHENOMENA

Roach, H. D., and Laufman, H.: Relationship Between Pulmonary Embolism and Pulmonary Infarction: An Experimental Study. Ann. Surg. **142:** 82 (July), 1955.

The authors produced thrombi in the blood stream of dogs, using bovine thrombin injected into the venous system, and studied the effects of the subsequent pulmonary emboli. Only in a small number of cases was infarction produced; when it was associated with atelectasis or pneumonia. Examination of the areas of involvement revealed changes, suggesting that the parenchyma had been abnormal before embolization.

The studies were repeated in dogs with distemper, because such animals usually had pneumonia. About half of this group showed frank hemorrhagic infarction in pneumonic lobes at postmortem examination.

In another group of dogs, the right lower lobe bronchus was ligated distal to the first branch of the bronchus and again pulmonary emboli were produced. It was found that limited decrease in ventilation did not materially influence the formation of infarction following embolization. However, additional ligation of the corresponding branch of the pulmonary artery, did increase the incidence of pulmonary infarction. Plugging the bronchus of the right lower lobe with cotton and ligation of two pulmonary vein branches produced infarction even without the formation of pulmonary emboli.

It was concluded that a firm, bland pulmonary embolism is more likely to lead to pulmonary infarction when infection, decreased aeration, or congestion is present in the lungs.

ABRAMSON

Williams, G.: Experimental Arterial Thrombosis. J. Path. & Bact. **69:** 199 (Jan.-April), 1955.

Thrombi were produced in the arteries of rabbits by damaging the endothelium and slowing the circulation by occluding with clamps. Both mural and occluding thrombi were produced and their organization was followed over a period of 84 days. Endothelium overgrows mural thrombi within 48 hours. Later the fibrin becomes hyalin and elastic fibers are laid down. Occluding thrombi show new vascular channels within 10 days. The fibroblastic cells in the thrombi are thought to be derived from endothelial cells. The similarities of organizing thrombi experimentally produced and naturally occurring in man are presented, and the role of this process as a factor in the etiology of atherosclerosis is pointed out by the author.

HARVEY

Jepson, R. P.: Peripheral Arterial Embolism. Brit. M. J. **2:** 405 (Aug. 13), 1955.

Attention is directed exclusively to emboli to the lower extremities, since in the opinion of the author "emboli in the upper extremities do not often constitute a surgical problem." Of 97 emboli (in 72 patients) 7 were to the aortic bifurcation, 9 iliac, 38 common femoral, 27 superficial femoral, 14 popliteal, 2 tibial. In 84 per cent of the patients there was atrial fibrillation, and in 16 per cent recent myocardial infarction.

Multiple emboli, including visceral ones, were frequent. Venous thrombosis was a complication in the embolized limb. There may be a time lapse before development of pain, and the pain may be located appreciably distal to the point of impaction.

In the differential diagnosis one must consider acute thrombophlebitis with extreme reflex arterial spasm (phlegmasis coerula dolens), arterial thrombosis, and dissecting aneurysm. Transmission of the thrust of each pulse through the clot to the fluid-filled vessel beyond may result in palpation of what seems like a normal pulse (Nordentoft's sign). Arterial spasm with embolism may have been exaggerated. Collapse of vessels, distal to the occlusion, may be due to lowering of intraluminal pressure according to the implications of Burton's "critical closing pressure."

Conservative treatment consists of maintenance of blood pressure, relief of pain by heavy sedation, and reflex relaxation of peripheral vasculature by heating the body. The limb should be kept horizontal at 25 C. Vasodilator drugs are ineffective.

The author advises embolectomy for embolus to the aortic bifurcation, following which heparin is not given, since he deems the risk of thrombosis less than of massive hematoma in the wound. Embolectomy is also recommended for femoral emboli but conservative measures are held most practical for lower emboli because of difficulties in making the necessary exposures.

MCKUSICK

Krause, S., and Silverblatt, M.: Pulmonary Embolism. Arch. Int. Med. **96:** 19 (July), 1955.

In recent years authors have frequently reported that pulmonary embolism is being underdiagnosed. These authors believe a high index of suspicion toward this complication is necessary. One should be especially aware of the frequency of pulmonary embolism as a complication of congestive heart failure. Apprehension, anxiety, and their concomitants should be considered "premonitory" symptoms of pulmonary embolism. These warnings, often confirmed by early electrocardiographic studies, should lead to the institution of appropriate, vigorous prophylactic treatment. Electrocardiograms should be obtained immediately and should be compared with control tracings, since they may be diagnostic or suggestive of pulmonary embolism when physical signs are absent. In the future, a higher incidence of successful removal of an obstructing embolus from the main pulmonary artery or its branches may be accomplished.

BERNSTEIN

Bassen, F. A.: The Variability of Prothrombin Time Determinations with "Standardized Thromboplastin Preparations". J. Mt. Sinai Hosp. **22:** 112 (July-August), 1955.

Prothrombin-time dilution curves were made with each of 4 widely used, commercial thromboplastin preparations, with prothrombin-free plasma as the diluent. The curves were quite similar, even though the 100 per cent plasma control times varied to some extent. The time of the more dilute mixtures could not be predicted from the time obtained on the whole plasma. Plasmas from Dicumarolized patients gave unpredictable results. Variations in time with one preparation bore no constant relationship with those of another; often the shortest times were obtained with the thromboplastin giving the longest control time. The various thromboplastin preparations for use on Dicumarolized plasmas could not be standardized by comparison with normal plasma diluted with barium sulfate-adsorbed plasma, because of differences between normal diluted plasmas and Dicumarolized plasmas.

In general, it was found that for therapeutic purposes, a 5 to 10 per cent prothrombin level is most satisfactory, and prothrombin times need not exceed 25 seconds, although bleeding has occurred at these levels.

CORTELL

Chiche, P., Jallat, H., and Acar, J.: Pulmonary Infarcts with Hemoptysis and Anticoagulant Therapy. Arch. mal. coeur **48:** 529 (June), 1955.

Referring to two personal observations, the authors discuss the problem of anticoagulant therapy in cases of pulmonary embolism complicated by massive hemoptysis. The first case, a 31 year old

patient with mitral stenosis, in whom anticoagulants were stopped subsequent to severe hemorrhage in the course of a pulmonary embolus, died from increasing heart failure. Autopsy revealed multiple pulmonary infarcts and severe hemorrhagic pulmonary edema. In another similar case, anticoagulant treatment was continued despite the occurrence of the hemorrhage, and this patient recovered.

Massive pulmonary bleeding in mitral disease subsequent to a pulmonary embolus appears to be attributed to pulmonary hypertension and development of abundant alveolar exudation rather than to the treatment with anticoagulants. Continuation of anticoagulants to prevent new emboli, together with all possible attempts to combat acute heart failure, is indicated in such difficult situations.

PICK

Foley, W. T.: The Use of Anticoagulants in Geriatrics. Geriatrics **10:** 299 (July), 1955.

The author states that anticoagulants have been used in the treatment of every type of intravascular thrombosis, and are used routinely in phlebitis and pulmonary embolism. Strong evidence has been presented in favor of their use in prevention of emboli from fibrillating and rheumatic hearts. The author believes that cases of myocardial infarction should be given anticoagulants, except where contraindicated. Investigations are being carried out relative to the use of anticoagulants in cerebral thrombi and emboli. Technics for administration of anticoagulants are given.

RINZLER

VASCULAR DISEASE

Franklin, R. B., and Mankin, J. W.: Arteriovenous Aneurysms of the Innominate Vessels. Arch. Int. Med. **96:** 413 (Sept.), 1955.

Arteriovenous aneurysm of the innominate vessels is a rare lesion. Two such cases have been found in the literature and a third is reported. The rarity of this lesion may be explained by the fact that a penetrating mediastinal injury, which might cause it, is usually fatal.

Three cases had the following features in common: (1) penetrating injury of the right upper chest resulting in internal hemorrhage, (2) latent period of 5 to 13 months between the original injury and recognition of an arteriovenous aneurysm, (3) a continuous murmur and thrill in the second right intercostal space, and (4) absence of the superior mediastinal syndrome, distinguishing this lesion from an arteriovenous aneurysm involving the aortic arch.

BERNSTEIN

Buttross, D. Jr., and Salatich, J.: Rupture of Aortic Aneurysm into the Pulmonary Artery. Report of a Case Proved by Cardiac Catheterization. Am. J. Med. **19:** 159 (July), 1955.

A case is reported in which erosion of an aneurysm of the aorta into the pulmonary artery, with production of a fistula between these 2 vessels, was proved by cardiac catheterization. The patient was alive and in a fair state of health 19 months after the episode occurred. The diagnosis and pathophysiology of this condition are discussed.

HARRIS

Bragdon, J. H., and Mickelsen, O.: Experimental Atherosclerosis in the Rat. Am. J. Path. **31:** 965 (Sept.-Oct.), 1955.

Effects of intravenous administration of serum lipoproteins in the rat are reported. Serum with high cholesterol content was obtained from rabbits that were fed cholesterol and was iniected intravenously into rats under a variety of conditions. Cholesterol values in the rat serum were obtained and the hearts and aortas of the rats were examined post mortem. An atheromatous-like change was found in the endocardium only, without any change in the aorta.

HARVEY

Thomson, A. P., and Marson, F. G. W.: Dissecting Aneurysm of the Aorta. Lancet **1:** 482 (March 5), 1955.

The authors describe in 2 cases a sign of dissecting aneurysm with external rupture: ecchymosis over the neck and upper thorax. The pulsating character of the pain was striking in 1 patient. One patient, aged 50, survived one year after external rupture and died finally of cerebral hemorrhage.

McKUSICK

Oester, Y. T., Davis, O. F., and Friedman, B.: Experimental Arteriopathy. Am. J. Path. **31:** 717 (July-Aug.), 1955.

The authors report on a method for producing arteriopathy in rabbits. Two hundred and ten adult albino rabbits divided into 3 groups were studied. One group served as controls, another was given daily intravenous injections of cholesterol suspension containing 40 mg. of cholesterol per Kg. of body weight for 11 days, and the third was subjected to daily intravenous injections of epinephrine, 40 gamma per Kg. of body weight, and intradermal injections of thyroxine, 0.15 mg. per Kg. of body weight for 11 days. All animals were sacrificed and the aortas examined grossly and microscopically. In the control group, only 1 animal showed sclerotic plaques on the aorta, whereas 23 of 32 animals treated with the cholesterol suspension, showed gross lesions of atherosclerosis. Forty-three of 48 animals treated with thyroxine-epinephrine injections showed medial necrosis but little intimal change. In another 6 animals, given combined treatment, severe arteriopathy of both types was seen in all. The etiology and pathogenesis of the changes are discussed.

HARVEY

DiGuglielmo, L., and Guttadavro, M.: Aortic Stenosis Associated with Aneurysmal Dilatation of the Ascending Aorta. Acta radiol. **43:** 437 (June), 1955.

This is a case report of a 32-year-old woman with a loud systolic murmur maximal at the aortic area, and a diastolic rumble extending upward from this area; the blood pressure was 110/90 in the upper extremities, 135/95 in the legs. There were calcified aortic valve leaflets on roentgenography, and a markedly dilated aortic arch extending from the valve region to just beyond the left subclavian artery demonstrable on angiocardiography.

The authors attributed the diastolic murmur to eddies of flow in the greatly dilated aorta; obviously the murmur was not due to aortic insufficiency. Two mechanisms could explain poststenotic dilatation: congenital weakness of the aortic wall and increased lateral pressure secondary to the rapid velocity of the jet flow from the ventricle into the aorta.

SCHWEDEL

Hulting, B., and Vendsalu, A.: Coarctation of the Aorta in Unusual Sites. Acta radiol. **43:** 453 (June), 1955.

The authors report on a case of coarctation of the aorta at the level of the diaphragm. The diagnosis was suggested by lower blood pressures in the lower extremities than in the upper, and confirmed by angiocardiography and aortography.

The authors present the important radiographic findings in cases previously reported, most of which were in the lower thoracic region, and others in the abdominal aorta. They suggest that in patients in whom the diagnosis is suspected on the basis of differential blood pressures, and who do not display evident collaterals in the upper thoracic region, atypical sites should be sought for by opacifying the descending aorta.

SCHWEDEL

Collens, W. S., Altman, M. A., and Stern, A. B.: A Motorized Treadmill: A Method for Quantitating Intermittent Claudication. Am. J. M. Sc. **230:** 190 (Aug.), 1955.

An objective test for measuring diminished walking capacity for patients with arterial occlusive disease is useful for clinical assessment of the disorder and for the evaluation of drug therapy. Such a test is provided by the use of a motorized treadmill and has the advantage of measuring the effort that elicits claudication sharply upon contraction of the muscles normally used in walking. The construction and method of use of the treadmill are reported, together with several case reports of its employment in the evaluation and treatment of patients with obliterative arterial processes.

SHUMAN

OTHER SUBJECTS

Shore, M. L., Zilversmit, D. B., and Ackerman, R. F.: Plasma Phospholipide Deposition and Aortic Phospholipide Synthesis in Experimental Atherosclerosis. Am. J. Physiol. **181:** 527 (June) 1955.

New Zealand rabbits were maintained for five months on diets supplemented with cholesterol dissolved in vegetable fat. These animals, and a control series, were then injected intravenously with native plasma phospholipids that were labeled with P^{32}. The resulting atheromatous thoracic aortas were examined for phospholipids by extraction with alcohol-ether and petroleum ether. Deposition of plasma phospholipids could account for less than one tenth of that detected in the atheromatous thoracic aortas. This emphasizes the point that most of the phospholipid in experimental atheromatosis is synthesized locally in the tissue of the aortas.

OPPENHEIMER

Tobian, L. Jr., and White, L.: Effect of a Low Sodium Diet on Electrolyte Composition of Arterial Wall. Am. J. Physiol. **181:** 599 (June), 1955.

Normal rats were maintained on a low-sodium diet. On a regimen like this, sodium in their aortas was reduced 12 per cent, and phosphorus was significantly elevated. In these animals, there was a very small increase in serum sodium. Water, magnesium, and potassium of aortas were unchanged when compared to those of a control group. Sodium restriction did not reduce blood pressure significantly. However, the author believes that the low-sodium content of aortas, after restriction of sodium in the diet, may be related to the tendency for blood pressure to be lower in such rats.

OPPENHEIMER

Abramson, J., and Tenney, B.: Cardiac Disease in Pregnancy. New England J. Med. **253:** 279 (Aug. 18), 1955.

The incidence of organic heart disease in pregnancy is said to range in various clinics from 0.3 to 2.0 per cent and the average death rate in cases of heart disease in pregnancy is between 2 and 3 per cent. The authors cite the report of Adams that the cardiac output increases by approximately 30 per cent immediately after delivery and is maintained at this level for the first few days postpartum. This rise is said to result from the extra blood squeezed from the maternal sinuses as the uterus contracts, and the release of the pressure of the uterus upon the great veins of the pelvis and lower extremities. The authors liken the effects of normal uterine contractions during labor to repeated small autotransfusions. Since no such gradual preparation for obliteration of the placental circulation occurs with abdominal delivery, this may explain, in part, the greater mortality rate

sociated with cesarean section in patients with art disease. The physiologic changes occurring the circulation during pregnancy are reviewed, d it is pointed out that the greatest strain upon e cardiovascular system occurs at 28 weeks of station and immediately postpartum. Recent ports are reviewed concerning the evaluation of e cardiac status during pregnancy, the occurrence congestive heart failure and subacute bacrial endocarditis. The onset of congestive heart ilure should be suspected if the vital capacity comes diminished at any period of the pregnancy, the pulse rate rises above 110 per minute, or if he respiratory rate exceeds 24 per minute. Weight ain during pregnancy in these patients should be mited to 18 pounds, and a sudden increase in eight may denote impending congestive heart ilure. If congestive heart failure occurs during regnancy, it should be treated in the usual way. The authors state that there are no established harmful effects of mercurial diuretics on the fetus. Quinidine or procaine amide may be used when indicated, since these drugs are not oxytocic. The management of labor and delivery is reviewed. Oxytocic agents should not be given routinely during the second stage, lest the contractility of the uterus be increased and greater amounts of blood than usual be forced into the blood stream. A loss of a moderate amount of blood in the third stage may be helpful, but the authors caution against excessive blood loss

It is said that valvuloplasty may be resorted to in mitral stenosis, but surgery should be avoided during pregnancy unless it seems to be a life-saving measure. After mitral-valve surgery, the patient may undertake future pregnancies with much less risk. In these patients, the cardiac status should be treated as if the patient were not pregnant and the obstetric problem as if she did not have heart disease.

ROSENBAUM

Kohn, L. A., and Nichols, E. B.: Interference with Uptake of Radioiodine Tracer during the Administration of Vitamin-Mineral Mixtures. New England J. Med. **253:** 286 (Aug. 18), 1955.

This study was undertaken because of the consideration that the supplementary intake of iodine in vitamin-mineral preparations may interfere with diagnostic studies of radioiodine uptake. At least 16 vitamin-mineral formulas commonly sold without prescription contain iodine, perhaps sufficient to block radioiodine uptake. Eight apparently euthyroid patients were given 2 capsules of Gevral daily, a preparation containing 0.5 mg. of iodine per capsule. A scattered response was observed, said to be expected on the basis of iodine from food, differences in absorption from the bowel, and a considerable range of avidity of the normal thyroid for iodine. However, in some subjects there was a definite blocking effect during the period of intake of the drug, with a tendency to recover the pretreatment level when the drug was stopped. It is recommended that patients being considered for determination of radioiodine uptake be questioned regarding their ingestion of compound vitamin-mineral preparations, and it is concluded that such preparations may explain unexpectedly low values in any extended series of observations.

ROSENBAUM

Meacham, G. C., and Weisberger, A. S.: Unusual Manifestations of disseminated Lupus Erythematosus. Ann. Int. Med. **43:** 143 (July), 1955.

One of the most important characteristics of disseminated lupus erythematosus (L.E.) is its simulation of other diseases. The most common clinical findings consist of fever, involvement of the skin and serous surfaces, alopecia, renal and ocular signs, adenopathy, splenomegaly, leukopenia, elevated serum globulin and predominance in females. However, early manifestations of this disease may be obscure. In this series of cases, thrombocytopenic purpura, hemolytic anemia, the presence of a circulating anticoagulant, a false-positive serologic test for syphilis, Raynaud's phenomenon, and intestinal perforation were seen either as the initial manifestation of the disease or during its course. The authors believe that a positive L.E. test (i.e., L.E. cells and rosettes) is diagnostic of disseminated lupus erythematosus. No false-positive L.E. tests were encountered. Negative L.E. preparations, however, do not rule out this disease, and it is often necessary to repeat the test. Disseminated lupus erythematosus may be present for long periods of time before a positive L.E. test is found, and the L.E. test is more frequently positive where there is an exacerbation of the disease. The authors subscribe to the theory that disseminated lupus erythematosus is due to hypersensitivity to an unknown agent.

WENDKOS

AMERICAN HEART ASSOCIATION, INC.

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APPLICATIONS FOR AHA RESEARCH SUPPORT NOW BEING ACCEPTED

Applications by research investigators for support of projects to be undertaken during the fiscal year beginning July 1, 1957 are now being accepted by the Association.

The application deadline for research fellowships and established investigatorships is September 15, 1956. Applications for grants-in-aid must be made by November 1, 1956.

Funds for Association supported research in the cardiovascular field are provided by public contributions to the annual Heart Fund. At least half of all funds received by the American Heart Association National Office are allocated to research. Approximately $15 million have been expended on research support by the Association and its state and local affiliates and chapters in the past 8 years.

Applications may be made for awards in the following categories:

Established investigatorships: Awarded for periods of up to 5 years, subject to annual review, in amounts ranging from $6,000 to $9,000 yearly, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators.

Research Fellowships: Awarded to young men and women with doctoral degrees for periods of 1 or 2 years to enable them to train as investigators under experienced supervision. Annual stipends range from $3,500 to $5,600.

Grants-in-aid: Made to experienced investigators to provide support for specified projects. Grants are made in varying amounts usually not exceeding $10,000.

The Association now maintains another and unique form of research support, the Career Investigatorship. This is given to a limited number of scientific investigators of unusual capacity and accomplishment to assure them of financial support throughout their productive lives. Career Investigators are selected on the initiative of the Research Committee and not by application.

Further information and applications may be obtained from the Medical Director, American Heart Association, 44 East 23 Street, New York 10, N. Y.

AHA SCIENTIFIC SESSIONS PROGRAM OUTLINED

A tentative program has been outlined for the American Heart Association's 29th Scientific Sessions to be conducted in Cincinnati in conjunction with the Association's Thirty-second Annual Meeting, October 26–31. The schedule, as drafted by the Program Committee of the Association's Scientific Council, includes original papers, panels and symposia, special memorial lectures, films and technical and scientific exhibits, most of which will be concentrated at the Cincinnati Music Hall beginning Friday evening, October 26, and continuing through Monday, October 29.

General sessions, which will be held on three mornings, will endeavor to include those papers of the widest interest to all professional disciplines attending the Scientific Sessions. Specialized Sessions, which will be afternoon events, will encompass those papers of particular interest to the members of the various sections and councils of the Association.

Memorial Lectures

The George E. Brown and Lewis A. Conner Memorial Lectures are to be presented on Saturday and Sunday mornings. Hugh Montgomery, M.D., of the University of Pennsylvania, has been invited by the Section on Circulation to give the Brown Lecture. Charles Rammelkamp, M.D., of the School of Preventive Medicine of Western Reserve University, has been asked by the Scientific Council to deliver the Conner Lecture.

The American Heart Association's Annual Dinner, will be held on Sunday, October 28,

at the Netherland Plaza Hotel. Two luncheon meetings also have been scheduled at the hotel, one to be conducted by the Council on Community Service and Education on Sunday, and the other to be given on Monday by the Council on Rheumatic Fever and Congenital Heart Disease.

The Monday luncheon will be followed by a Scientific Session at which papers on rheumatic fever and congenital heart disease will be presented. The Community Service event will be followed by a program of interest to both professional and lay audiences. This program will be in addition to the presentations made under the auspices of the Community Service and Education Council as part of the Scientific Sessions. These presentations are to consist of original papers to be reviewed by the Program Committee of the Scientific Council on the same basis as will papers in the areas of interest of the other sections and councils.

It is estimated that there will be facilities at the Music Hall in Cincinnati for approximately 40 scientific exhibits and 88 technical exhibits. Commercial firms interested in presenting technical exhibits should address inquiries to Stephen K. Herlitz, Exhibit Manager, 280 Madison Avenue, New York. A special medical film program is now being arranged.

The Schedule

Here is the tentative schedule of Scientific Sessions:

Friday evening, October 26: Sessions on instrumentation, electrocardiography, ballistocardiography and vectorcardiography.

Saturday, October 27: Morning—General session sponsored by Sections on Clinical Cardiology and Cardiovascular Surgery; Brown or Conner Lecture.

Afternoon—Panel or symposium arranged by Section on Clinical Cardiology; simultaneous specialized sessions sponsored by Sections on Basic Science and Circulation (jointly) and by Section on Cardiovascular Surgery.

Sunday, October 28: Morning—General session sponsored by Sections on Clinical Cardiology, Basic Science and Circulation; Brown or Conner Lecture.

Afternoon—Panel or symposium arranged by Section on Clinical Cardiology; simultaneous specialized sessions sponsored by Sections on Basic Science and Circulation (jointly) and by the Council for High Blood Pressure Research.

Monday, October 29: Morning—General session sponsored by Section on Clinical Cardiology and Council for High Blood Pressure Research; symposium on "Cardiac Rehabilitation" sponsored by Council on Community Service and Education.

Afternoon—Panel or symposium arranged by Section on Clinical Cardiology; simultaneous specialized sessions sponsored by Sections on Basic Science and Circulation (jointly) and by Council on Rheumatic Fever and Congenital Heart Disease.

Review of Papers

Papers submitted for presentation at the Scientific Sessions will be reviewed by the Program Committee of the Scientific Council and by the program committees of the individual sections and councils. This review will begin immediately after the deadline for submission of abstracts, June 15.

COMMITTEE APPOINTED TO REVIEW HAVANA CONGRESS ABSTRACTS

A committee has been appointed by E. Cowles Andrus, M.D., Chairman of the Association's Scientific Council, to review abstracts submitted by United States physicians and research investigators for presentation at the Inter-American Congress of Cardiology in Havana, November 11 to 17. This procedure is required under the regulations of the Inter-American Cardiological Society which provide that papers must be submitted through the national cardiologic society of the country in which the authors reside.

To be eligible for consideration, United States papers must be sent to the Association by July 1. They should not exceed 200 words in length. Time allotted for the actual presentation of each paper will be 10 minutes, with an additional 5 minutes for discussion.

The program of the Inter-American Congress will include panel discussions, symposia, lec-

tures, presentation of scientific papers, scientific and technical exhibits and motion pictures. Registration fee for the entire Congress is $25, and associate membership registrations are provided for members of the registrant's family at $10 each. Money orders should be sent to the Congress Treasurer, Dr. Luis Ortega Verdes. All communications regarding the Congress, except abstracts, should be addressed to the Fifth Inter-American Congress of Cardiology, Apartado 2108, Havana, Cuba.

SECOND EUROPEAN CARDIOLOGY CONGRESS, SEPTEMBER 10–14

The Second European Congress of Cardiology will be held in Stockholm, Sweden, September 10 to 14. United States physicians are welcome to participate. The Association will be officially represented. Fuller information may be obtained from Dr. Karl Erik Grewin, Secretary General, Second European Congress of Cardiology, Sodersjukhuset, Stockholm, Sweden.

1955 HIGH BLOOD PRESSURE RESEARCH PROCEEDINGS

The Proceedings of the 1955 Annual Meeting of the Association's Council for High Blood Pressure Research have been published in book form, and are now available from the Association. The volume contains all 8 papers presented in the meeting at Cleveland last November, together with verbatim transcripts of the ensuing discussions. The Proceedings offer a concentration of the latest knowledge in the field of hypertension, particularly with regard to its neurovascular aspects.

REVISED DIAGNOSTIC GUIDE ON CONGENITAL DEFECTS ISSUED

A newly revised edition of the booklet, *Diagnosis of Cardiac Defects in General Practice*, is now available from the Association. The edition was prepared by Regina Gluck, M.D., Assistant Clinical Professor of Pediatrics, the Children's Medical Service of Bellevue Hospital.

The revision reflects the many advances made in knowledge and in clinical experience with regard to diagnosis, management and treatment of congenital defects. Particular attention is paid to surgical procedures which were either not known or not clinically tested when the previous edition was issued in November, 1954. Thus, for example the new edition lists among operable conditions, *atrial and septal defects*, which could not be so listed previously.

As the title implies, the booklet is designed primarily for the general practitioner. As an additional aid to the practitioner, the new edition includes a bibliography of selected references.

Physicians may obtain copies of *Diagnosis of Cardiac Defects in General Practice* through their local Heart Association or through the American Heart Association, 44 East 23 Street, New York 10, N. Y.

NEW VISUAL KIT DEMONSTRATES CARDIOVASCULAR SYSTEM

The second kit in the AHA Cardio-Views series is available from the Association. The new kit, entitled, *The Cardiovascular System*, consists of 24 three-dimensional color slides depicting various parts of the heart including the valves, the coronary artery system, the aorta and the cerebrovascular system.

The kit is designed for both medical school and postgraduate teaching and for individual study by the physician. Cost of the kit is $5.00. A special viewer, necessary for all Cardio-Views kits, is available for $1.25. Kits and viewers may be obtained from the American Heart Association, 44 East 23 Street, New York 10, N. Y.

CARDIOVASCULAR RESEARCH TRAINING PROGRAM TO BE HELD AT GEORGIA

A postgraduate cardiovascular research and training program, jointly sponsored by the American Heart Association and the National Heart Institute of the U. S. Public Health Service, will be conducted at the Departments of Physiology and Pharmacology, Medical College of Georgia, Augusta, Ga., starting on July 1. A stipend of $3,400 plus $350 for each dependent and certain expenses will be provided to participants. Inquiries and requests for application forms should be addressed to either of the directors of the program, Dr. W. F. Ham-

lton or Dr. P. Ahlquist, Medical College of Georgia, Augusta, Ga.

AHA FILM LIBRARY ACQUIRES THREE MEDICAL FILMS

Three new motion pictures of interest to medical audiences have been added to the AHA Film Library. These films are:

Streamline Flow in Veins, produced in color and with sound by the Wellcome Film Division of Burroughs Wellcome and Co. The film presents a demonstration by Dr. D. A. McDonald of the Department of Physiology, St. Bartholomew's Hospital Medical College, London, of streamlined and turbulent blood flow in a glass model. It runs 15 minutes on 16 mm. film.

Living Microscopic Blood Vessels: Normal and Pathological Conditions, produced in color by Drs. Brenton R. Lutz and George R. Fulton of the Department of Biology of Boston University. The film demonstrates the use of the hamster cheek pouch as a "living laboratory" for gross and microscopic investigation of a variety of peripheral vascular phenomena. It runs 30 minutes on 16 mm. film.

Tetralogy of Fallot, produced in color and with sound by E. R. Squibb and Sons. Starting with a brief review of the embryonic development of the heart, it shows the associated anomalies of the tetralogy, and the procedures for surgical correction. Running time is 30 minutes on 16 mm. film.

All three films are suitable for medical students as well as physicians. The *Tetralogy of Fallot* is also suitable for student and graduate nurses. Information on rental may be obtained from the AHA Film Library, 13 East 37 Street, New York 16, N. Y.

MEETINGS CALENDAR

July 23–26: International Congress of Developmental Biology, Providence, R. I. Professor Paul Weiss, Rockefeller Institute for Medical Research, 66th St. and York Ave., New York 21, N. Y.

July 27–31: Second International Symposium on the Cellular Basis of Differentiation, Providence, R. I. Professor Paul Weiss, Rockefeller Institute for Medical Research, 66th St. and York Ave., New York 21, N. Y.

August 13–16: National Medical Association, New York. John T. Givens, M.D., 1108 Church St., Norfolk 10, Va.

September 3–9: Sixth Congress of the International Society of Hematology, Boston. Dr. S. Haberman, 3301 Junius St., Dallas, Tex.

September 6–8: American Association of Obstetricians and Gynecologists, Hot Springs, Va. F. R. Lock, Bowman Gray Medical School, Winston-Salem, N. C.

September 9–13: Tenth International Congress of the International College of Surgeons (including Twenty-first Annual Congress of the U. S. and Canadian Sections), Chicago. Karl Meyer, M.D., 1516 Lake Shore Dr., Chicago, Ill.

September 10–14: American Congress of Physical Medicine and Rehabilitation, Atlantic City. Frances Baker, M.D., 1 Tilton Ave., San Mateo, Calif.

ABROAD

July 22–27: Eighth International Congress of Pediatrics, Copenhagen. Eighth International Congress of Pediatrics, Domus Medica, 12A Kristianiagade, Copenhagen, Denmark.

July 22–28: Eighth International Congress of Radiology, Mexico City. Dr. Jose Noriega, Secretary General of Congress, Tepic 126 (2e piso), Mexico, D. F. 7.

July 30–August 4: Twentieth International Physiological Congress, Brussels. Professor J. J. Reuse, Faculté de Médicine et de Pharmacie, 115 Boulévard de Waterloo, Brussels, Belgium.

August 1–6: First International Congress of Human Genetics, Copenhagen. The University Institute for Human Genetics, Tagensvej 14, Copenhagen, Denmark.

August 19–23: Fourth International Congress on Diseases of the Chest, Cologne. Mr. M. Kornfeld, American College of Chest Physicians, 112 Chestnut St., Chicago 11, Ill.

August 20–24: Second International Congress of Physical Medicine, Copenhagen. Dr. Svend Clemnesen, Kommunehospitalet, Copenhagen, Denmark.

September 10–14: Second European Congress of Cardiology, Stockholm. Professor K. E. Grewin, Södersjukhuset, Stockholm, Sweden.

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